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PUBL. JUNE 1952

# The Unipolar Electrocardiogram

A CLINICAL INTERPRETATION

BY

Joseph M. Barker, M.D., F.A.C.P.

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As Reviewed in POSTGRADUATE MEDICINE, October, 1952

"The Author . . . has succeeded in presenting the subject . . . in a comprehensive and simple manner. The book is profusely illustrated with many electrocardiographic tracings . . . and many unusual electrocardiographic patterns. There is also a large number of diagrammatic figures explaining the subject in detail. This fine work should be very useful to the physician and student."

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**MAURICE C. PINCOFFS**

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*Thirty-fourth Annual Session*

**THE AMERICAN COLLEGE  
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**Meetings**—all to be held at Convention Hall.

**Program**—will appear in the February, 1953, issue of this journal, and will be printed separately and distributed to all members of the American College of Physicians and non-member physicians whose names are on the mailing list. Program will consist of General Scientific Sessions, Symposia, Color Televised Clinics, Review Lectures, Panel Discussions and Clinical-Pathological Conferences. Speakers and participants will be carefully selected authorities in the several fields of Internal Medicine and allied specialties.

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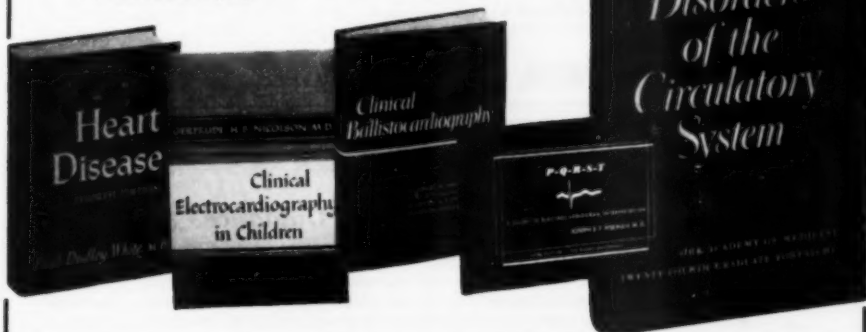
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1. Watson, E. M., and Thompson, M. W.: *Am. J. Digest. Dis.* 18:326, 1951.

2. Wilson, J. L.; Root, H. F., and Marble, A.: *J.A.M.A.* 147:1526 (Dec. 15) 1951.



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**Bibliography:** 1. Barach, A.L., et al.: Bull. New York Acad. Med. 28:353 (June) 1952.  
2. Flippin, H.F., et al.: Report distributed at the Chicago Session of the A.M.A. (June) 1952.  
3. Segal, M.S., et al.: GP, in press.

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1. Fremont, R. E.; Rimmerman, A. B., and Shafiel, H. E.: *Postgrad. Med.* 10:216, 1951.

2. Rimmerman, A. B., et al: *Am. Pract. & Digest Treat.* 2:100, 1951.

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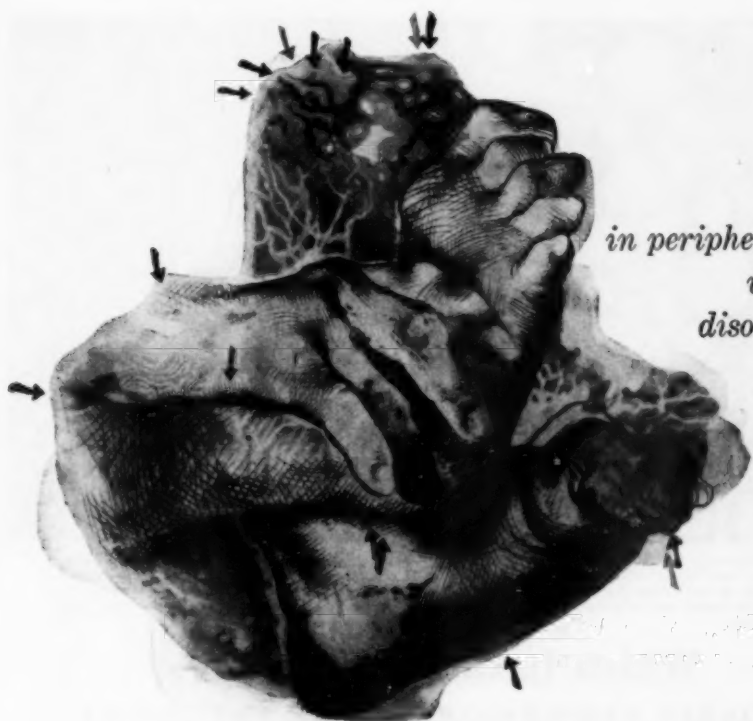
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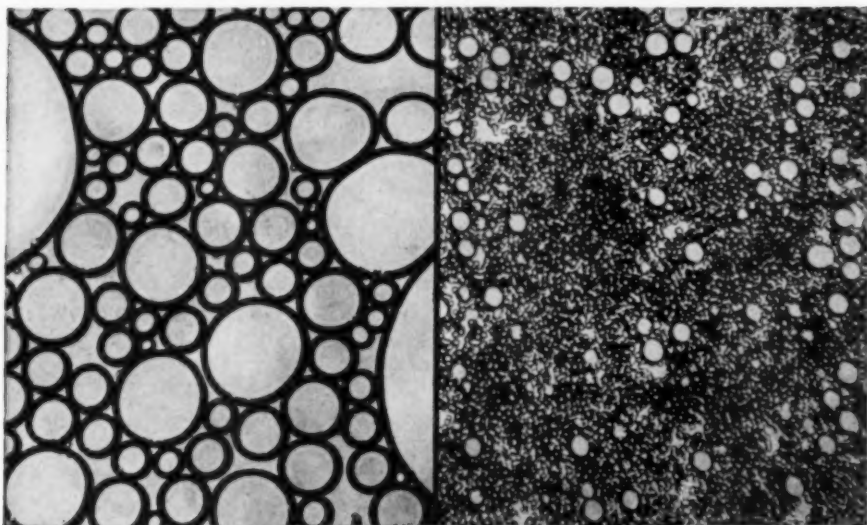
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2. Heller, E. M.: The Treatment of Essential Hypertension. *Canad. Med. Assn. Jour.*, 61:293-299, Sept., 1949.

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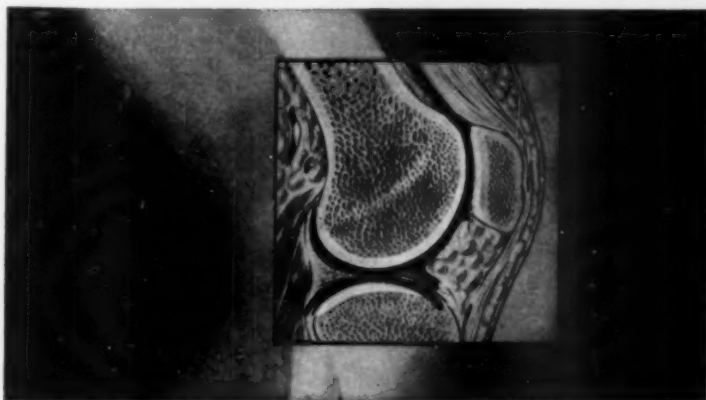
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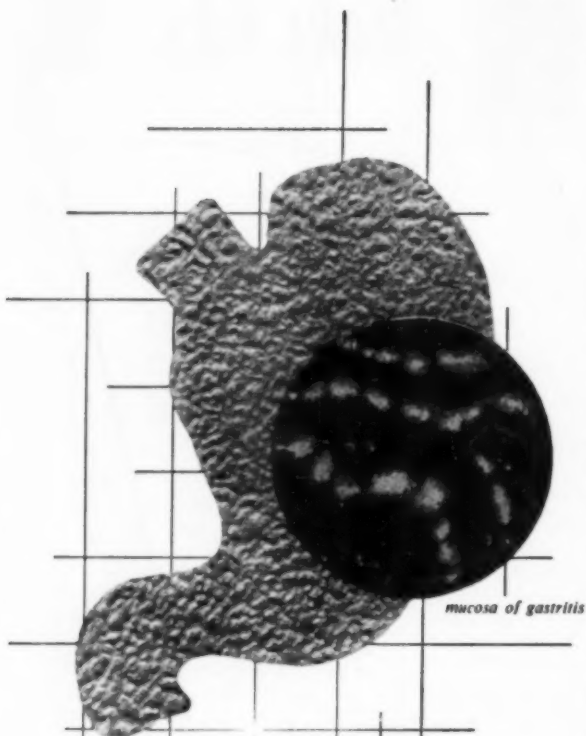
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\*Talkov, R. H., Ropes, M. W., and Bauer, W.: *The Value of Enteric Coated Aspirin*. N.E.J. Med. 242:19 [Jan. 5] 1950.



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*IODINE	0.7 mg.	PANTOTHENIC ACID	3.0 mg.
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ZINC	2.6 mg.		
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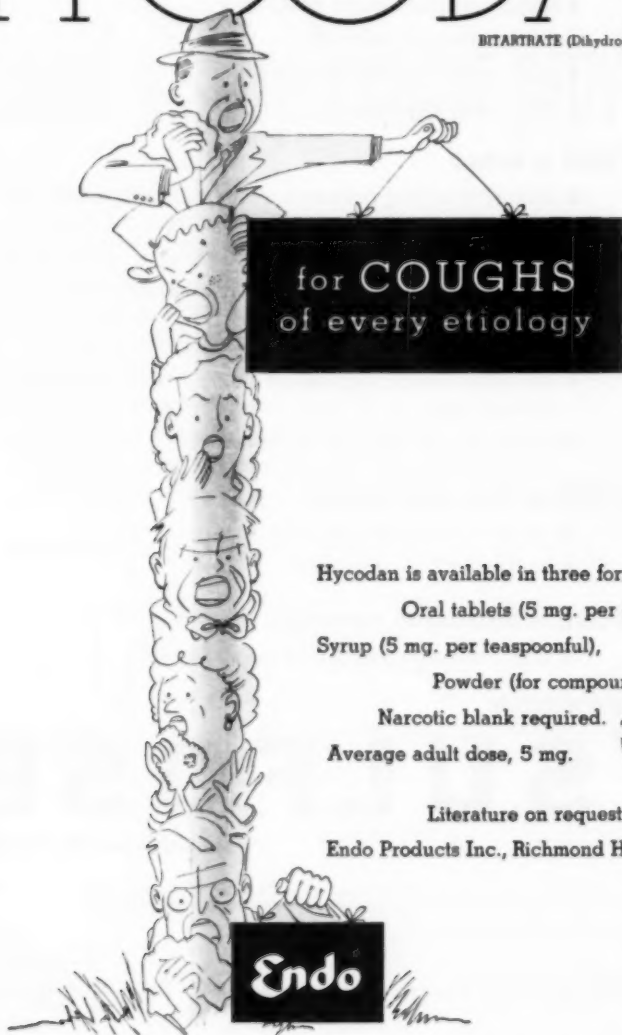
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# ANNALS OF INTERNAL MEDICINE

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NUMBER 6

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## **HYPERTHYROIDISM—AN EVALUATION OF TREATMENT WITH ANTITHYROID DRUGS FOLLOWED BY SUBTOTAL THYROIDECTOMY \***

By ELMER C. BARTELS, M.D., F.A.C.P., *Boston, Massachusetts*

SINCE soon after the discovery of the new antithyroid drugs it appeared that these substances did not have specific curative properties for definitive treatment of hyperthyroidism, we began to use them as preoperative agents. Therefore, most of our patients with hyperthyroidism received one of these agents until a euthyroid state was established and then a radical subtotal thyroidectomy was done. This began a new era in the surgical management of hyperthyroidism.

In the past eight and one-half years, 2,400 patients with hyperthyroidism have been treated by this plan. The experience with this sizable group of patients and a careful follow-up study of the first 1,800 patients form the basis of this report. All of these patients were cared for by two physicians (the author and his colleague, Dr. George O. Bell), which led to uniformity in care and treatment. Nine general surgeons of the Lahey Clinic performed the operative procedures (thyroidectomy), employing the Lahey operative technic, which includes the careful dissection and exposure of the parathyroid glands and the recurrent laryngeal nerves.

These 2,400 cases include patients who had primary hyperthyroidism (diffuse goiter, 80 per cent) and adenomatous goiter with hyperthyroidism (20 per cent). The ages of the patients ranged from six years to 77 years; 10 per cent of the patients were over 60 years of age. Ten per cent of the patients were classified as having thyrocardiac disease, a combination of hyperthyroidism and associated heart disease, many of whom had profound congestive heart failure when initially seen. Antithyroid treatment, followed by subtotal thyroidectomy, was considered for all hyperthyroid patients ir-

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\* From the Symposium on Thyroid Disease presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 23, 1952.

From the Department of Internal Medicine of the Lahey Clinic, Boston.

respective of the severity of the disease, age of the patient or state of physical depletion when first examined. A few patients with irreversible heart disease (neglected thyrocardiacs) died before the antithyroid treatment became effective, and a few patients were refused surgical treatment because of associated malignant disease, advanced cirrhosis of the liver or malignant hypertension. These latter patients have been maintained on treatment with one of the antithyroid drugs.

#### ANTITHYROID AGENTS USED

Since the introduction of the first antithyroid agent, thiouracil, many allied preparations (thiourea, thiobarbital, aminothiouracil, methylthiouracil, propylthiouracil, meprociol, Itrumil, Tapazole and others) have become available and have been given clinical trial in an effort to find the drug which is most effective and which has the lowest incidence of reactions.

Thiourea and aminothiouracil were abandoned because of their disagreeable taste. After propylthiouracil was introduced, thiouracil, thiobarbital and methylthiouracil were discarded because of the high incidence of reactions, 10 per cent (in 450 patients), 28 per cent (in 28 patients) and 13 per cent (in 100 patients), respectively. When the beneficial effectiveness and low reaction rate (1.6 per cent) of propylthiouracil were established, it became the drug of choice and was used in the treatment of approximately 1,500 of the 2,400 patients in this group. However, even when propylthiouracil is used, the danger of agranulocytosis is always present; it occurred in 1 per cent of cases. In this series there were no deaths from agranulocytosis, but in the literature<sup>1</sup> four fatalities from agranulocytosis induced by propylthiouracil were reported, which indicates the seriousness of this complication. The skin reactions which developed usually necessitated withdrawal of propylthiouracil therapy.

Our experience with Tapazole (1-methyl-2-mercaptoimidazole) is based on the treatment of 214 patients. There were 16 reactions, an incidence of 7.5 per cent. Skin manifestations represented the chief problem, especially when high doses (40 to 50 mg. daily) were used. Administration of Tapazole had to be discontinued in most cases, although a few patients tolerated it in reduced dosage or when given in combination with one of the antihistamine substances (pyribenzamine). Those patients who did not tolerate Tapazole were given propylthiouracil.

Severe arthralgic pains developed in the legs and arms of one patient who received Tapazole, and hospitalization was necessary. When Tapazole was discontinued the pains were relieved; propylthiouracil was then given and was well tolerated. In one patient there was a marked depression of the polymorphonuclear cells (figure 1). In this case agranulocytosis had developed during the previous administration of propylthiouracil, and granulocytopenia of 15 per cent resulted when Tapazole was given. The drug was then withdrawn. The literature contains reports<sup>2</sup> of one case of nonfatal

agranulocytosis and one case of granulocytopenia which occurred during Tapazole therapy. I have been advised<sup>3</sup> of two fatalities which occurred in California from agranulocytosis following the use of Tapazole.

To date, experience with the use of the antithyroid drugs indicates that these substances cannot be given without danger, and, therefore, continuous observation and repeated blood counts are necessary if serious depressive blood changes and possible fatalities are to be avoided. A completely safe antithyroid drug has not as yet been developed.

Itrumil (iodothiouracil), another relatively new antithyroid agent, was used in only a small series (34 cases), since we found it to be of limited use

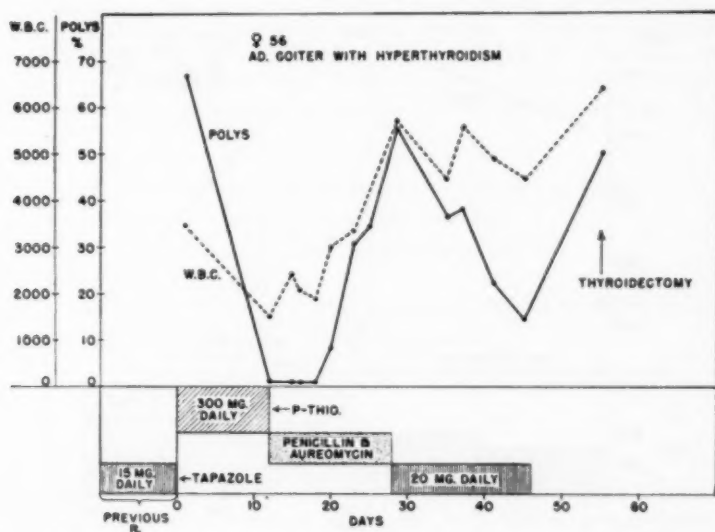


FIG. 1. Agranulocytosis developed in this case while the patient was receiving propylthiouracil. The blood returned to normal. Although Tapazole had not caused blood changes previously, 18 days after again starting Tapazole treatment the granulocytes decreased to 15 per cent.

and ineffective in patients who had large, diffuse goiters (figure 2). This is apparently the result of the presence of iodine in the molecule, which leads to the same difficulty observed when an antithyroid agent and iodine are given simultaneously to a patient who has a large, diffuse, hyperplastic goiter. Improvement does occur initially due to the iodine, but a euthyroid state cannot be accomplished in spite of continued treatment even in sizable doses. This led to the use of Itrumil only in those patients who had small diffuse goiters who required therapy for periods of only three to four weeks. In some patients it was used during the last three weeks of treatment, since

it brought about the same involutional changes in the thyroid gland as those that follow administration of iodine. McClintock and Lyons,<sup>4</sup> proponents of Itrumil, admitted that with the use of this agent it was difficult to control hyperthyroidism in some patients who suffered from toxic diffuse goiters. Starr<sup>5</sup> and his associates also admitted that some patients were resistant to Itrumil therapy. It is the iodine in Itrumil (iodothiouracil) which probably is responsible for this blocking effect. The observation by Bondy<sup>6</sup> that Itrumil produces a very pronounced rise in the protein-bound iodine, not noted with other antithyroid drugs, could explain the occasional ineffectiveness of this drug.

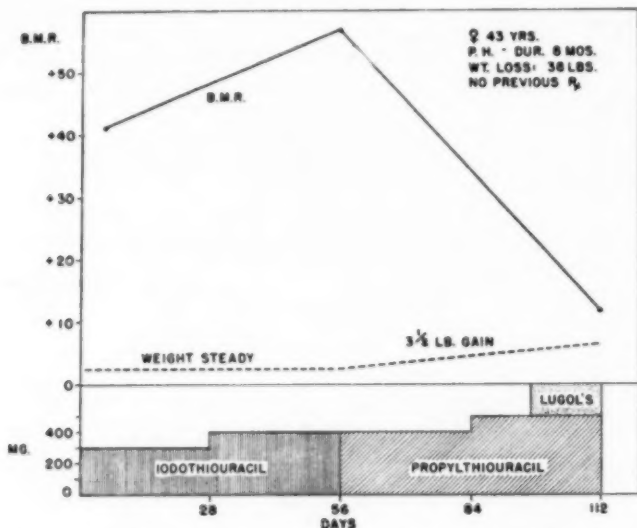


FIG. 2. In this case the basal metabolic rate failed to drop and the patient did not gain weight while on iodothiouracil (Itrumil) in doses of 300 to 400 mg. for 56 days. When propylthiouracil was given the basal metabolic rate promptly fell and reached normal after 56 days of treatment.

*Dosage:* Two hundred to 400 mg. of propylthiouracil were given daily, the size of the dose being dependent upon the size of the goiter, larger doses for large goiters. On rare occasions, a dose of 600 mg. daily was given to patients with very large adenomatous goiters, without an increase in the incidence of reactions. The dose of methylthiouracil was similar to that of propylthiouracil. Tapazole<sup>7,8</sup> was found to be 10 times as active as propylthiouracil; the effective dose was 20 to 40 mg. daily. There appeared to be little choice between propylthiouracil and Tapazole as antithyroid agents, since both were found to be effective agents with low reaction incidence.

## THE ESSENTIALS OF PROPER PREOPERATIVE USE OF ANTITHYROID DRUGS

Certain essentials were strictly adhered to in all cases (table 1). The first principle is the establishment of the proper diagnosis—primary hyperthyroidism or adenomatous goiter with hyperthyroidism—since with these data, the duration of treatment was gauged. Patients who had adenomatous goiter required a period of treatment approximately twice as long as those with primary hyperthyroidism. Initially, the choice of the drug was determined by those agents available. Full, effective doses were used during the entire period of treatment, and only when the response to treatment was greater than expected (which rarely occurred) was the dose reduced. All patients were told of the possibility of reactions and advised to seek care should untoward signs or symptoms develop. Check-up examinations, which included a white blood count and a differential count, were carried out every two to three weeks. When reactions occurred short of full antithyroid control, the patients were given another antithyroid drug. In only

TABLE I  
Essentials of Proper Preoperative Use of Antithyroid Drugs

1. Distinction between types of hyperthyroidism
  - a. Primary hyperthyroidism
  - b. Adenomatous goiter with hyperthyroidism
2. Antithyroid drug
  - a. Proper daily dose
  - b. Awareness of specific reactions with indications for shifting to another antithyroid drug
3. Duration of therapy (carefully individualized)
  - a. Continue until euthyroid state is attained
  - b. Maintain in euthyroid state for a period—at times advisable
4. Addition of Lugol's solution
  - a. Antithyroid effect
  - b. Involutional effect
5. Avoidance of overtreatment (myxedema)

one case was a euthyroid state not established before thyroidectomy was performed. This was the patient (figure 1) in whom agranulocytosis developed from propylthiouracil and severe granulocytopenia from Tapazole.

The duration of treatment was carefully individualized. In addition to bringing about a euthyroid state in those patients whose bodies were depleted from long-standing hyperthyroidism (especially those with thyrocardiac disease), treatment was continued several months to as long as one year before it was concluded that thyroidectomy could be done without risk. Patients who were treated for long periods of time were observed for the development of myxedema; strict attention was given to the plasma cholesterol determinations (not basal metabolic rates). Thyroidectomy was never undertaken when myxedema was present because myxedema greatly increases postoperative complications.

Lugol's solution was given to patients with primary hyperthyroidism during the three weeks immediately preceding operation. Occasionally, patients who had severe hyperthyroidism with diffuse goiters (primary hyper-

TABLE II  
Mortality Following Thyroidectomy

No. Cases	Number	Mortality	Per Cent
2400	5		0.20

thyroidism) were given iodine during the first seven days because of its rapid antithyroid effect. Iodine was not given to patients who had adenomatous goiters.

In addition to meticulous preoperative antithyroid therapy, careful surgical and anesthetic technics were followed. These patients were carefully observed during the immediate postoperative period and if respiratory embarrassment developed, a tracheotomy was performed. During the last two to three years, so-called "prophylactic tracheotomy" has been done at the time of the thyroidectomy in those thyrocardiac patients with decreased cardiac reserves in whom it was feared that even a minor degree of anoxemia would be harmful. A tracheotomy done at the time of the thyroidectomy is a relatively simple procedure; it does not increase the postoperative mortality, and increases the hospital stay by only a few days. We are certain that this procedure was life-saving in some of our severely ill patients with low cardiac reserve.

#### OPERATIVE MORTALITY

There were five postoperative deaths (table 2) in this series of 2,400 hyperthyroid patients. All five (table 3) had associated cardiac disease. The first patient died suddenly on the second postoperative day, although he appeared perfectly well up to the time of death. At necropsy, myocardial fibrosis was found. The second patient died suddenly during the thyroidectomy from what appeared to be cardiac arrest. In the third, fourth and fifth patients, respiratory embarrassment developed postoperatively as a result of laryngeal edema and the patients died before the seriousness of the con-

TABLE III  
Data on Deaths Following Thyroidectomy

Case	Age Sex	Type of Hyper- thyroidism	Duration of Hyper- thyroidism	BMR		Duration of Treat- ment	Associated Disease	Time and Cause of Death
				Initial	Preop.			
1	65 M	Primary	3 years	23	4	3 mos.		2nd postop. day, myocardial fibrosis
2	63 F	Adenomatous	1 plus years	43	16	2 mos.	Hypertension	Cardiac arrest
3	61 F	Primary	3 months	65	9	4 mos.	Cardiac failure	3rd postop. day, tra- cheal obstruction
4	53 F	Primary	3 years	—	12	2 mos.	Rheumatic heart disease, auricular fibrillation. Hypertension	10 hrs. postop., tra- cheal obstruction
5	35 F	Primary	3 years	70	14	2 mos.		1 hr. postop., tracheal obstruction. Nec- ropsy, acute myo- carditis (rheu- matic?)

dition was appreciated and an emergency tracheotomy could be done. Two of the patients (cases 3 and 4) died in the operating room while preparations were being made for a tracheotomy. These last three deaths occurred before our present plan of prophylactic tracheotomy in bad risk thyrocardiac patients was instituted. Case 5, in addition to a tracheal obstruction which occurred soon after operation, was found at necropsy to have acute myocarditis which was thought by the pathologist to be rheumatic in type. This was not appreciated before operation, as the blood counts did not reveal an infection. These three patients had such severe myocardial weakness that they could not tolerate even a minimum of myocardial anoxemia resulting from tracheal narrowing. All of these patients had adequate antithyroid treatment (two to five months) and at the time of thyroidectomy were in a euthyroid state.

#### PREGNANCY AND HYPERTHYROIDISM—THYROIDECTOMY<sup>9</sup>

Twenty-seven patients in this group of 2,400 patients were pregnant. The principle followed was to treat these pregnant patients who were hyper-

TABLE IV  
Hyperthyroidism and Pregnancy Results Following Antithyroid Treatment and Thyroidectomy during Pregnancy

Number of normal pregnancies		21
Resulting healthy children	23	
Number of abnormal pregnancies		6
Outcome		
Abortion at 5 months	1	
Premature deliveries	2	
Stillborn at 8 months	1	
Died 4 hours later	1	
Stillbirths	2	
Cesarean at term	1	
(died 8 hours later)		
Total pregnancies		27
Fetal loss		22%

thyroid in the usual way if they were in the first or second trimester of pregnancy; those in the third trimester were not submitted to thyroidectomy until after delivery. Of the 27 patients (table 4), 21 went to term and had normal deliveries, with 23 healthy children. In six patients, the outcome was variable and appeared completely unrelated to the antithyroid treatment or the thyroidectomy. The fetal loss for the entire group was 22 per cent. Following a study of the first 18 patients who had hyperthyroidism during pregnancy and in whom the fetal loss was 28 per cent, my colleague, Dr. George O. Bell, suggested that iodine and desiccated thyroid be given during the interval between thyroidectomy and delivery. Nine patients have been so treated; eight of the nine patients have had full-term normal deliveries, with nine normal children. There was but one fetal loss, a fetal mortality of 11 per cent which is a significant lowering of fetal loss.

That the antithyroid drugs are not harmful in pregnancy has also been

shown by Astwood,<sup>10</sup> in that, of his patients who were taking propylthiouracil, 15 became pregnant and came to delivery; three infants (20 per cent) were premature, but there was no fetal loss. Our experience and that of Astwood are not in accord with the opinion of Dailey and Benson<sup>11</sup> who, in their review of the problem of hyperthyroidism and pregnancy, do not favor the use of thiouracil compounds but recommend subtotal thyroidectomy preceded only by iodination. On such a plan there was a 38 per cent fetal loss; three of the deaths resulted from therapeutic abortions. Their results do not prove their plan of handling these cases to be very successful.

Our experience with hyperthyroid patients who were pregnant indicates that antithyroid therapy followed by thyroidectomy is a safe procedure during the first and second trimesters of pregnancy. Overtreatment with the antithyroid drugs must be avoided. This is best accomplished by serial determinations of the plasma cholesterol as a guide to proper dosage, since the plasma cholesterol level is more informative during pregnancy than the basal metabolic rate. Thyroidectomy must not be undertaken until a euthyroid state is established. After operation, iodine (10 drops) and desiccated thyroid (0.5 gr.) should be administered daily. The desiccated thyroid (0.5 gr.) is given to prevent any possible ill effect on the fetus of postoperative hypothyroidism, which condition frequently occurs, at times in a preclinical state, during the first or second month after thyroidectomy.

#### OBSERVATIONS AFTER THYROIDECTOMY

All of our patients were advised to have periodic determinations of the basal metabolic rate. An attempt was made to obtain a basal metabolic rate every three months for the first year and then yearly for four years. By means of these check-up examinations, these patients were closely watched over a five year period. Chiefly of medical interest are the results of the check-up studies covering the problems of (1) postoperative tetany; (2) recurrent hyperthyroidism, and (3) postoperative myxedema.

*Postoperative Tetany* (table 5): Signs or symptoms of tetany developed after operation in 70 of 2,300 patients, an incidence of 3 per cent. All patients were carefully questioned concerning the symptoms of tetany. A Chvostek test was carried out routinely on all patients, and frequently a

TABLE V  
Postoperative Tetany

Type of tetany	Cases	Per Cent
Permanent	16	0.69*
Transient	42	1.8*
No follow-up obtained	8	
Follow-up too short	4	
Total	70	

\* In first 2,300 patients.

Trousseau test was done. The incidence of tetany, particularly mild, transient tetany, is directly related to whether a search is made for it, since patients with mild tetany frequently do not mention the presence of numbness and tingling of the fingers and lips; they are willing to accept these symptoms as an expected postoperative complaint. Severe tetany will, of course, always lead to troublesome complaints.

Postoperative tetany began during the first to the sixth day, usually on the first or second day. The duration of transient tetany was from five days to four years, thus leading to the encouraging conclusion that tetany may be transient even if it lasts three to four years. Transient tetany lasted for an average of three months in 42 of the 70 patients (1.8 per cent of 2,300 patients); 32 of this group of 42 patients (76 per cent) had had tetany for less than three months. Sixteen cases (0.69 per cent of 2,300 patients) are classified as permanent tetany. Since the duration of tetany in these 16 cases is from one to six years, it is possible that some of the cases later may be reclassified as having transient tetany.

The initial level of serum calcium was not found to be a guide as to whether the tetany would be transient or permanent. Also, tetany occurred as commonly in patients who had primary hyperthyroidism as in those who had adenomatous goiter. This was to be expected, since tetany is the result of surgical removal or injury to the circulation of the parathyroid glands. The incidence of tetany was found to be increased in those patients who had previously undergone surgical procedures on the thyroid gland, as indicated by the observation that 25 per cent of the patients with permanent tetany and 33 per cent of those with transient tetany had had previous thyroidectomy.

*Recurrent Hyperthyroidism:* The incidence of recurrent hyperthyroidism was carefully studied in the first 1,800 patients in this series of 2,400 cases. Sixteen hundred seventy patients had had periodic metabolic studies for a period of three to eight years, and recurrent hyperthyroidism developed in 33 patients of this group. All of these patients had primary hyperthyroidism, confirming the clinical impression that in cases of hyperthyroidism due to an adenomatous goiter, the disease will not recur if a subtotal thyroidectomy is done. Of these 33 patients, seven had previously had operations on the thyroid, and thus had recurrent disease when initially seen. The age of the 33 patients ranged from 11 to 69 years, averaging 36 years. All of the patients were thought initially to have severe hyperthyroidism, judging by height of basal metabolic rate, weight loss, pulse rate and degree of activation. The sex factor in recurrent disease was not contributory.

On analysis of these 33 cases, it was found that seven could be classified as having persistent disease, since hyperthyroidism had been present from the time of the thyroidectomy to the time of the metabolic check-up which revealed its presence. In three cases the hyperthyroidism was recurrent initially; only the larger thyroid remnant was removed, thus permitting the

remaining remnant to increase in size. The remaining four patients with presumably persistent disease were among the first to receive antithyroid drugs preoperatively, and before we had had sufficient experience to reach a decision as to how radical the thyroidectomy should be in these cases. It was soon agreed that the operation should be as radical as in the usual iodine treated cases.

In 22 of the 33 patients who had recurrent hyperthyroidism and in whom the data were adequate, the disease recurred in from six months to eight years after the thyroidectomy, with an average of three years. The size of the goiter removed was not a factor in recurrent disease, since only five had more than 75 gm. of tissue removed. As a rule, the enlargement of a remnant preceded the symptoms of hyperthyroidism, although occasionally the remnant and symptoms developed simultaneously.

Further treatment of hyperthyroidism was needed by all 33 patients. Additional thyroid tissue was removed in 12 cases (36 per cent); 18 patients (54 per cent) are being maintained on Lugol's solution; all of these had Grade I to II remnants; one patient was given x-ray treatment, with remission; one patient with large remnants is being maintained on antithyroid treatment, and one patient was given radioactive iodine. This experience indicates that the treatment of recurrent hyperthyroidism must be carefully selected for the individual patient. All of these patients are well at the present time.

*Postoperative Myxedema:* The incidence of postoperative myxedema was determined in the first 1,000 cases of this group, of which 942 could be followed. There were 69 cases of postoperative myxedema, an incidence of 7.3 per cent. Thirteen patients, or 1.3 per cent, had transient myxedema, and 49, or 5.2 per cent, had permanent myxedema. Myxedema rarely occurred in patients with adenomatous goiter (in only three of the 69 cases—4 per cent). Of the entire group of 942 patients, 20 per cent had adenomatous goiter with hyperthyroidism. Myxedema developed in twice as many of the patients who had a second thyroidectomy for recurrent primary hyperthyroidism as in those who had an initial thyroidectomy. Fifty-six patients were classified in the latter group and 10 patients in the former. All ages were represented, from six to 68 years. Neither the severity of the hyperthyroidism nor the duration of the disease was a factor in the development of myxedema after operation. A review of the pathologic data revealed that 12 patients (17 per cent) had strumitis in addition to primary hyperplasia, an incidence significantly higher than that found in patients who had strumitis but did not develop myxedema after operation (2.8 per cent). Carcinoma of the thyroid was found in three cases: in two it was associated with primary hyperthyroidism and in one with adenomatous goiter. Röntgen therapy following thyroidectomy most likely played the major rôle in producing the myxedema. Postoperative wound infection did not play a rôle, as only two patients had this complication. Five patients (7 per cent) had tetany in addition to postoperative myxedema, indicating that the

extent of surgery is a major factor in the development of postoperative myxedema.

It was found that myxedema can develop at any time up to five years after thyroidectomy, although in 46 per cent this complication developed within the third month and in 73 per cent within the first year. Most patients had symptoms indicating myxedema; 20 per cent were completely asymptomatic, and the diagnosis was made on objective evidence alone, or with the aid of the basal metabolic rate or plasma cholesterol. Twenty-eight per cent had a basal metabolic rate of higher than minus 20 per cent. The plasma cholesterol was less than 200 mg. per 100 c.c. in 16 per cent of cases. It was the drop in the cholesterol level during thyroid medication in these cases which showed these initial low levels to be correct.

The daily dose of thyroid required to control the myxedema varied widely; 71 per cent required 1 gr. or less, and no patient required over 2 gr. a day. Patients who had coronary sclerosis with angina pectoris were maintained on small doses,  $\frac{1}{4}$  grain, and the two children under 10 years of age received only  $\frac{3}{4}$  grain daily. In all cases the myxedema was completely controlled.

Most of the patients with transient myxedema had the condition for one year or less, although two patients were able to discontinue treatment at the end of two years and one patient at the end of three years. This lends support to the plan of withholding treatment at least once or twice during the first year, the second or even the third year, to confirm the need for continued thyroid treatment. After the third year, the myxedema can be considered to be fixed and treatment will be necessary throughout the patient's life.

#### SUMMARY

The antithyroid drugs have aided greatly in the preoperative treatment of hyperthyroidism, as proved by their use in 2,400 patients who had all degrees of the disease. Many effective antithyroid drugs are available, propylthiouracil and Tapazole being the most popular at the present time. The antithyroid drugs must be administered under careful observation, since serious blood changes are a real danger. When these drugs are used preoperatively, patients must be treated individually, and no patient should be submitted to thyroidectomy until a euthyroid state is reached and all evidences of hyperthyroidism and resulting physical depletion are overcome. If this is accomplished, a low operative mortality is possible. In this series of 2,400 cases there were five deaths, a mortality of 0.2 per cent.

Antithyroid drugs can safely be given to pregnant patients with hyperthyroidism if myxedema is avoided preoperatively and postoperatively until the time of delivery.

Postoperative tetany occurred in 3 per cent of cases, and was permanent in 1.8 per cent. In all of these patients the tetany was controlled with powdered calcium lactate alone or in combination with vitamin D.

Hyperthyroidism recurred, even after radical thyroidectomy, in 33 of 1,670 cases studied, an incidence of 1.9 per cent. These patients were treated selectively; in most patients the disease was controlled either by the daily administration of iodine or by a second operation, removing the recurring thyroid remnants.

Postoperative myxedema occurred in 7.3 per cent of the first 942 cases studied; in 5.2 per cent of cases it was permanent. Myxedema was found to develop any time up to the fifth year after operation and also to be transient up to the third year. In most patients, however, postoperative myxedema developed within the first year and remained permanent if thyroid was required after the first year. Desiccated thyroid controlled all cases of postoperative myxedema; the usual dose was 1.5 grains or less.

#### BIBLIOGRAPHY

1. Colwell, A. R., Jr., Sando, D. E., and Lang, S. J.: Propylthiouracil-induced agranulocytosis, toxic hepatitis, and death, *J. A. M. A.* **148**: 639-641 (Feb. 23) 1952.
- Livingstone, H. J., and Livingstone, S. F.: Agranulocytosis and hepatocellular jaundice; toxic reactions following propylthiouracil therapy, *J. A. M. A.* **135**: 422-425 (Oct. 18) 1947.
- Juliari, B., and Harris, T. L.: Fatal agranulocytosis occurring during propylthiouracil therapy; report of a case, *J. A. M. A.* **139**: 646 (Mar. 5) 1949.
- Beebe, R. T., Propp, S., McClintock, J. C., and Versaci, A.: Fatal agranulocytosis during treatment of toxic goiter with propylthiouracil, *Ann. Int. Med.* **34**: 1035-1040 (Apr.) 1951.
2. Croke, A. R., and Berry, J. W.: Agranulocytosis occurring during methimazole ("Tapazole") therapy; report of a case, *J. A. M. A.* **148**: 45-47 (Jan. 5) 1952.
- Wilkins, R. B., Cleveland, F. E., and King, R. L.: Granulocytopenia from Tapazole—case report, *Bull. Mason Clin.* **5**: 123-127 (Dec.) 1951.
3. Boehme, E. J.: Personal communication.
4. McClintock, J. C., and Lyons, J. A.: Iodothiouracil in the treatment of hyperthyroidism, *J. Clin. Endocrinol.* **11**: 111 (Jan.) 1951.
5. Catz, B., Petit, D. W., and Starr, P.: Therapeutic studies in hyperthyroidism; sodium 5-iodo-2-thiouracil, *J. Clin. Endocrinol.* **11**: 978-995 (Sept.) 1951.
6. Bondy, P. K.: The effect of iodothiouracil on the serum protein-bound iodine, *J. Clin. Endocrinol.* **11**: 1406 (Nov.) 1951.
7. Bartels, E. C., and Sjogren, R. W.: 1-Methyl-2-mercaptoimidazole; a new active anti-thyroid agent, *J. Clin. Endocrinol.* **11**: 1057-1062 (Oct.) 1951.
8. Hallman, B. L., and Bondy, P. K.: Experience with methimazole (Tapazole) in the treatment of hyperthyroidism, *Am. J. Med.* **11**: 724-729 (Dec.) 1951.
9. Bell, G. O.: Hyperthyroidism, pregnancy and thiouracil drugs, *J. A. M. A.* **144**: 1243-1246 (Dec. 9) 1950.
10. Astwood, E. B.: The use of antithyroid drugs during pregnancy, *J. Clin. Endocrinol.* **11**: 1045-1056 (Oct.) 1951.
11. Dailey, M. E., and Benson, R. C.: Hyperthyroidism in pregnancy, *Surg., Gynec. and Obst.* **94**: 103-109 (Jan.) 1952.

## THE DISTURBANCE OF THE NORMAL BACTERIAL ECOLOGY BY THE ADMINISTRATION OF ANTIBIOTICS WITH THE DEVELOPMENT OF NEW CLINICAL SYNDROMES \*

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EVIDENCE is accumulating to show that the complex balance which exists among microorganisms constituting the normal flora of the body is disturbed by the prolonged administration of the newer antibiotics. This may result in the development of secondary vitamin deficiencies or the evolution of new infectious disease syndromes.

The importance of the normal microbiologic flora in man was not appreciated until it was disorganized by the administration of the newer antibiotics. The basic phenomenon is not new, and biologists dealing with parasitic diseases of plants are familiar with the importance of the normal flora of the soil and its influence on the increase or decrease of the parasitic species.<sup>1, 2, 3</sup>

Biologists have known for many years that the struggle for survival among animal species has its counterpart in the world of microscopic organisms. Some species of microorganisms maintain their superiority by a rapid rate of multiplication, while others poison competitors with the waste products of their metabolism. To supplement such simple maneuvers as consuming all of the available food or fouling the environment with waste products, certain species have learned to synthesize organic poisons, which attack the protoplasm of their enemies, or antibiotics, which disrupt specific enzyme systems essential for the maintenance of life. In other words, bacteria and fungi were employing antibiotics as offensive weapons long before they were discovered by man.

This antagonism between microorganisms is seen sometimes between different strains of a single species but more often between species of different genera. Most of the known antibiotics which kill bacteria are produced by fungi, while antibiotics derived from bacteria kill fungi. Unfortunately, these potent fungicides are toxic for man and have a very limited use in therapy.

The precarious balance maintained among the microorganisms of the soil is easily disturbed by an increase or decrease in temperature, moisture, sunlight, acidity or organic content of the soil.<sup>3</sup> Man has better control over his external and internal environment; consequently, the saprophytic and com-

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menal organisms which live normally on or in his body are less subject to radical changes. When environmental changes do occur in the body, the organisms respond in a manner analogous to the changes observed in the soil. There is a well known disease of childhood, initiated by dehydration, which may be classified as an environmental syndrome.

#### SUMMER DIARRHEA IN CHILDREN

This disease of infants, now called "summer diarrhea," was known to previous generations of physicians by the graphic name of cholera infantum. During periods of hot weather, with or without a coincidental infection, some children become dehydrated and reduce the amount of digestive enzymes in their small intestines. Colon bacilli multiply in the partly digested food in the duodenum and jejunum and produce organic acids which initiate both vomiting and diarrhea.<sup>4</sup> The loss of fluids accelerates the dehydration, and a vicious cycle is established which often results in the death of the infant in 24 to 48 hours unless the fluids and electrolytes are replaced and the colon bacilli are deprived of fermentable substances.

#### SEPTICEMIA FOLLOWING IRRADIATION

Another example of an infectious syndrome caused by bacteria which are normal inhabitants of the body is observed following total body radiation. This phenomenon was studied by Miller and his associates<sup>5</sup> in mice which had been irradiated by x-rays, but there is a good possibility that the same syndrome will occur in man following irradiation from atomic bombs. In the animal experiments the intestinal mucosa was damaged, after which colon bacilli and other commensals from the intestinal tract invaded the blood stream and killed the animals. Streptomycin reduced but did not eliminate mortality in these experiments.

#### THE ANTIBIOTIC EFFECT OF THE NORMAL BACTERIAL FLORA

The infant is free of bacteria when it begins its passage through the birth canal. Some bacteria are acquired during birth, and within a few days of birth the child has acquired a flora which is practically identical with that of the adults in its environment.<sup>6</sup> It is not known why certain types of bacteria have become adapted to specific areas of the body, but it was probably achieved by competition in a manner analogous to the establishment of a normal flora in the soil. As in the soil, the normal flora resents the invasion of foreigners. Saprophytic organisms from the air, soil and water are being introduced on and into the body almost constantly, but they do not survive in competition with the normal inhabitants.

Under favorable conditions, the normal saprophytic flora of the soil prevents the multiplication of bacterial and fungal microorganisms which infect plants. The normal commensal flora of man may prevent the establishment of species parasitic for man. One example of this type of protection was presented by Thompson and Shibuya in 1946.<sup>7</sup> These investigators found

that the common alpha streptococci, which are always present in varying numbers in the upper respiratory tract, produced an antibiotic which killed virulent diphtheria bacilli.

#### ORAL LESIONS FOLLOWING LOCAL APPLICATIONS OF PENICILLIN

Complications in the oral cavity are unusual following either oral or parenteral therapy with penicillin, but local treatment with lozenges, powders or sprays may be followed by increased redness or edema and secondary infections with yeasts and molds which give the clinical picture of "hairy tongue" or "black tongue."<sup>8</sup> The penicillin is not irritating in the concentrations employed. Although it has been found that penicillin may accelerate the growth of a few species, such as *Candida albicans* var. *stellatoidea*<sup>9</sup> and *Pseudomonas aeruginosa*,<sup>10</sup> the primary mechanism is probably the elimination of the normal inhibitors of yeast and molds, such as the gram-positive cocci. Many of the gram-negative bacilli are inhibited also by the concentrations of penicillin used locally but not by the amounts which appear in the oral cavity following parenteral injections or oral ingestion of penicillin. In some instances, local hypersensitivity to penicillin may develop and add to the complications. We have seen one patient whose oral tissues apparently were sensitized by local penicillin therapy. The inflamed oral mucous membranes returned to normal after therapy was discontinued, but became red and swollen again after a single dose of penicillin by injection.

#### CHANGES IN THE BRONCHIAL AND PULMONARY FLORA FOLLOWING PARENTERAL PENICILLIN

Almost everyone is familiar with the changes which follow penicillin therapy for chronic bronchitis, chronic bronchiectasis and chronic pulmonary abscess. Often the initial improvement is dramatic, with reduction in fever and sputum and improvement in appetite. But after a few weeks of continuous therapy the sputum increases again, frequently changes color, and is occasionally more profuse than before therapy was instituted. Smears and cultures reveal that the original predominantly gram-positive flora has been replaced by gram-negative bacilli of the type usually found in the intestinal tract. *Klebsiella pneumoniae*, the old Friedländer's bacillus, and *Pseudomonas aeruginosa*, the old *Bacillus pyocyaneus*, are the most dangerous of the secondary invaders. We are now isolating occasionally a pink colony from these chronic cases which has been identified as *Serratia marcescens*, the old *Bacillus prodigiosus*. This supposedly nonpathogenic organism has apparently become pathogenic, but fortunately can be eliminated in most instances with aureomycin therapy.

We do not know the cause of this alteration in flora, but must assume that the predominantly gram-positive organisms were preventing the implantation, or at least the multiplication, of these gram-negative bacilli from the intestinal tract until they in turn were eliminated by penicillin therapy.

## THE EFFECT OF COMBINED PENICILLIN AND STREPTOMYCIN THERAPY

In general, streptomycin is more effective against gram-negative bacilli than gram-positive cocci, and occasionally severe or even fatal infections with cocci occur during streptomycin therapy.<sup>11</sup> Practically all bacteria are eliminated by the simultaneous administration of both penicillin and streptomycin or aureomycin.<sup>12</sup>

The influence of alternate and simultaneous administration of penicillin and streptomycin on the organisms found in the sputum of a patient with chronic bronchiectasis is illustrated by the following case.

## CASE REPORTS

*Case 1.* A young girl of 16 years with moderately severe bilateral bronchiectasis was admitted to the hospital for study. She produced daily about 60 c.c. of purulent sputum which had a definite yellow color. Smears from the sputum showed numerous gram-positive cocci, and cultures revealed *Micrococcus pyogenes* var. *aureus*, the old *Staphylococcus aureus*, in almost pure culture. Penicillin was administered parenterally and by aerosol for 10 days. The sputum decreased rapidly and was only 10 c.c. in amount at the end of seven days. Then the color changed from yellow to green and increased to 30 c.c. daily during the next three days. Smears at this time revealed a flora of gram-negative bacilli, and the cultures yielded a heavy growth of *Esch. coli*. Penicillin was discontinued and streptomycin was given parenterally and by aerosol for 10 days. The sputum decreased to about 5 c.c. by the seventh day and then returned to 20 c.c. by the tenth day. As the sputum increased it became yellow in color, and the cultures again revealed the presence of *Micrococcus pyogenes* var. *aureus*.

Both penicillin and streptomycin were administered parenterally and by inhalation for 10 days. The sputum decreased to 5 c.c., lost its purulent character, and became grayish in color and mucoid in consistency. Cultures grew out numerous colonies of *Candida albicans* and *Aspergillus fumigatus*. Therapy was discontinued because we feared a superimposed mycotic infection of the lungs.

A bilateral basal lobectomy was advised but was refused by the patient and her family. After the antibiotic therapy was discontinued, the original micrococcal flora was reestablished and the sputum was again purulent in consistency and yellow in color. Six months later the patient developed a large metastatic abscess of the brain and died after an attempt at drainage.

This case illustrates the antagonism between the pyogenic cocci of the respiratory tract and the gram-negative bacilli from the intestinal tract. It also suggests that both groups of bacteria can suppress the yeast and mold-like fungi which are not inhibited by penicillin, streptomycin, aureomycin, chloramphenicol or terramycin.

## SECONDARY MYCOTIC INFECTIONS FOLLOWING ANTIBIOTIC THERAPY

The fungi which appear as secondary invaders following antibiotic therapy are a part of the normal microbiologic flora of the body. *Candida albicans* can be isolated from the saliva of approximately 20 per cent of normal individuals, the skin of 30 per cent,<sup>13</sup> the intestinal tract of 33 per cent<sup>14</sup> and the vagina of 15 per cent.<sup>15, 16</sup> Various species of *aspergillus*, *penicillin*,

*cryptococcus*<sup>17</sup> and *geotrichum*<sup>14</sup> are normal inhabitants of the body but occur with less frequency than *Candida albicans*. Fungi which are not carried by man but acquired from some source in nature, such as those causing blastomycosis, histoplasmosis, coccidioidomycosis, nocardiosis and sporotrichosis, have not been found as secondary invaders following antibiotic therapy. *Actinomyces bovis*, which is found as a normal inhabitant of the mouth, fortunately is susceptible to the action of penicillin and the other antibiotics.

Before the introduction of antibiotics in therapy, *Candida albicans* was known to produce thrush in infants and debilitated adults, bronchitis and occasionally pneumonitis, but almost never invaded the internal organs. Following prolonged treatment with the newer broad coverage antibiotics, or with the combination of penicillin and streptomycin, infections with *Candida albicans* are encountered much more frequently. Serious infections of the mouth and pharynx,<sup>18, 19, 20</sup> vagina<sup>16</sup> and lungs<sup>8</sup> have become quite common, and fatal infections following the invasion of the internal organs are being recognized.<sup>21</sup>

#### EFFECTS OF ANTIBIOTICS ON THE SYNTHESIS OF VITAMINS BY INTESTINAL BACTERIA

Although some of the bacteria constituting the normal flora of the intestinal tract may be destroying vitamins,<sup>22</sup> most of them are engaged in synthesizing vitamin K<sup>23</sup> or the various members of the B complex group.<sup>24, 25, 26</sup> Most of the synthesis occurs in the colon, and the amount of absorption has been questioned. It seems probable that some vitamins are absorbed from the colon, and even a small supplement from this source may be of great importance in individuals consuming a diet which contains minimal amounts of the B complex vitamins. Most of the studies on vitamin synthesis by intestinal bacteria have been in animals which were fed large amounts of the poorly absorbable sulfonamides, such as sulfaguanidine,<sup>27</sup> but the more powerful broad coverage antibiotics should be more effective in eliminating vitamin synthesizing bacteria from the intestinal tract.

Infectious diseases usually affect the patients' appetites and reduce the consumption of food and concomitant vitamins. When the appetite and digestion are disturbed, as is so often the case following therapy with aureomycin, chloramphenicol and terramycin, the intake of food and vitamins is restricted more severely. The situation becomes even more complicated when the ecologic balance in the intestinal tract is upset by antibiotics, and a diarrhea results from an overgrowth of *Candida albicans* or by a coccus resistant to the antibiotic.<sup>20</sup> Prolonged therapy may induce frank vitamin deficiencies,<sup>28</sup> while partial and intermittent deficiencies may result in the development of focal infections.<sup>29</sup>

In case 2, prolonged treatment with aureomycin was followed by the development of a severe secondary pulmonary moniliasis and a vitamin deficiency characteristic of pellagra.<sup>28</sup>

*Case 2.* A 60 year old white married female patient was treated with aureomycin for over a month for a chronic pulmonary pneumonitis of unknown etiology. During the latter part of the treatment, the pulmonary symptoms grew worse and the patient became disoriented. An application had been made for admission to a psychiatric hospital when she was admitted to the Duke Hospital for medical treatment. Her oxygen absorption was so poor that she was receiving oxygen therapy when admitted, and oxygen was continued for three weeks after admission. The temperature was elevated between 101 and 102° F., and there were râles of all types throughout both lungs. X-ray films showed extensive, almost confluent fibrosis and pneumonitis in both lungs. *Candida albicans* (*Monilia albicans*) was present in large numbers on cultures made from her sputum. *Micrococcus pyogenes* (*Staphylococcus aureus*) was present also. Vaccines were prepared from her own organisms and skin tests performed.<sup>30</sup> Immediate reactions of the urticarial wheal type appeared at the site of the vaccine injection after 30 minutes. The reactions were indistinguishable from those usually seen in asthmatic patients following the injection of pollens or other allergens. The immediate reactions disappeared within an hour and were followed by tuberculin-like reactions which reached their height between 24 and 48 hours.<sup>30</sup> The fungus and coccus vaccines were mixed in equal proportions and then diluted 1,000 times. Desensitization was attempted with this 1:1,000 dilution of the mixed vaccines. Potassium iodide was not administered because of the fear that sudden resolution of areas of infiltration might liberate an excess amount of fungal and bacterial antigen in a highly allergic patient.

Improvement occurred in her vital capacity concurrently with the passage of time and with the administration of the vaccine. The sputum decreased in amount and the râles in her lungs became less numerous. There was some decrease in the pulmonary infiltrations, but the clinical improvement was more dramatic than that seen by x-ray. After the third week, she was relatively comfortable without oxygen therapy.

The patient's type of disorientation resembled that seen in pellagra, although the characteristic lesions of face, hands and feet were absent. One should remember that the easily recognized lesions of pellagra occur after direct exposure to the sun or some other source of radiant heat, and are absent in the winter months and even in the summer if the patient has been confined indoors.<sup>28</sup> Other signs of the pellagra syndrome are less dramatic but more reliable, since they may be found at any time of the year. A careful inspection showed that the skin over the nose and about the ala nasi was abnormally dry, and small concretions of altered sebum were plugging the orifices of the sebaceous glands. This gave a rough, sandpaper-like texture to the skin over the affected area.<sup>31</sup> The skin over the elbows, knees and ankles was thickened and pigmented but not infected.<sup>28</sup> The mucous membranes of the mouth and vagina were red and edematous and covered with patches of white pseudomembranes. Smears from the pseudomembranous areas showed an abundance of Vincent's organisms, which are frequently present as secondary invaders in pellagra, and cultures revealed a heavy growth of *Candida albicans*, which is a common secondary infection following prolonged therapy with aureomycin and other broad coverage antibiotics. We concluded that the patients had developed pellagra with psychosis and moniliasis of the lungs, mouth and vagina after prolonged treatment with aureomycin.

A commercial mixture of vitamins, containing nicotinic acid amide, thiamin, riboflavin, pyridoxine and ascorbic acid was injected intravenously each day for the next seven days. Oral vitamin therapy was substituted for the intravenous injections after the seventh day. The oral and vaginal lesions disappeared in about 10 days; the lesions of dyssebacia<sup>31</sup> over the nose and forehead disappeared in the same length of time. Her mental state improved after two weeks and she was practically normal after two months. The pigmented, hyperkeratotic skin lesions over the elbows, knees and ankles improved slowly, but the areas were still pigmented at the time of discharge.

This patient was not cured; she was discharged with her original undiagnosed pulmonary infection, but we did cure the new syndrome induced by the prolonged administration of aureomycin. We have seen other, but less severe cases of B complex deficiencies following therapy with aureomycin, chloramphenicol, terramycin and various combinations of the powerful antibiotics.

### DISCUSSION

The normal microbiologic flora of man is varied and complex but seems to have been stabilized by a long process of evolution in such a manner that the organisms have a happy home and man is not injured. The microorganisms, bacteria and fungi are properly designated commensals and not saprophytes. They are antagonistic to and effectively prevent pure saprophytes from joining the normal ecologic flora. They may play an important rôle in preventing the invasion of small numbers of parasitic species, although proof of this effect has been found in only one instance.<sup>7</sup>

Apparently constant and deadly warfare is carried on between gram-positive cocci and gram-negative bacilli, and between both these groups and the yeast and moldlike fungi. The precarious balance maintained by the normal ecologic flora is upset easily by the administration of antibiotics. Often the type of microbial alteration can be predicted if the name of the antibiotic and the duration of treatment are known. When the ecologic flora is changed radically, and commensal organisms multiply rapidly in an area of the body not normally inhabited by that organism, or in an area where multiplication has been inhibited previously by biologic antagonists, then commensal organisms may produce disease without the necessity of a specific lowering of the resistance of the patient. These are the new infectious disease syndromes referred to in the introduction.

Secondary vitamin deficiencies may follow the prolonged administration of the newer antibiotics. The deficiencies may result partly from the decreased consumption of vitamin carrying food and partly from a reduction or elimination of intestinal bacteria which normally synthesize vitamins.

The opinion expressed by Keefer<sup>32</sup> and the author of an editorial in this Journal<sup>33</sup> regarding the dangers inherent in the prolonged administration of antibiotics is supported by this review.

### CONCLUSIONS

1. Prolonged therapy with penicillin suppresses or eliminates gram-positive bacteria and stimulates directly or indirectly the multiplication of gram-negative bacilli.
2. Prolonged therapy with relatively large doses of streptomycin may suppress the gram-negative bacilli and stimulate the growth of gram-positive cocci. This effect is not so constant as the reversed one induced by penicillin therapy.
3. The prolonged administration of both penicillin and streptomycin simultaneously, or of aureomycin, chloramphenicol or terramycin may sup-

press both gram-positive cocci and gram-negative bacilli to such a degree that the fungi of the yeast and mold types from the normal ecologic flora multiply and produce disease in the mouth, vagina, bronchi, lungs and intestinal tract.

4. Vitamin deficiencies of the B complex type, including the syndrome of pellagra, may follow the prolonged administration of the newer broad coverage antibiotics.

5. Antibiotics should not be used in mild and ill defined infections because a drug sensitivity may develop which will prevent the subsequent use of the antibiotic in a major illness. The dangers of inducing sensitivity seem to be greatest when the antibiotic is applied locally.

6. The newer antibiotics, with broad coverage spectrums, should not be administered for more than one week at a time unless the etiologic agent causing the infection has been identified and the indications for prolonged therapy are obvious.

7. A complete vitamin supplement, with special emphasis on the B complex group, should be given to all patients receiving prolonged therapy with the newer antibiotics.

#### BIBLIOGRAPHY

1. Waksman, S. A.: Antagonistic relations of microorganisms, *Bact. Rev.* **5**: 231 (Sept.) 1941.
2. Wolf, F. A., and Wolf, F. T.: *The fungi*, vol. 2, 1947, John Wiley and Sons, New York, p. 279.
3. Garrett, S. D.: Ecology of the root inhabiting fungi, *Biol. Reviews* **25**: 220 (April) 1950.
4. Davison, W. C.: The duodenal content of infants in health, and during and following diarrhea, *Am. J. Dis. Child.* **29**: 743 (June) 1925.
5. Miller, C. P., Hammond, C. W., and Tompkins, M.: The incidence of bacteremia in mice subject to total body x-radiation, *Science* **111**: 540 (May 19) 1950.
6. Smith, D. T.: Bacterial ecology and flora of the normal body, in Zinsser's *Textbook of bacteriology*, 1942, Appleton-Century-Crofts, New York.
7. Thompson, R., and Shibuya, M.: The inhibitory action of saliva on the diphtheria bacillus: the antibiotic effect of salivary streptococci, *J. Bact.* **51**: 671 (June) 1946.
8. Woods, J. W., Manning, I. H., Jr., and Patterson, C. N.: Monilia infections complicating the therapeutic use of antibiotics, *J. A. M. A.* **145**: 207 (Jan. 27) 1951.
9. Foley, G. E., and Winter, W. D., Jr.: Increased mortality following penicillin therapy of chick embryos infected with *Candida albicans* var. *stellatoidea*, *J. Infect. Dis.* **85**: 268 (Nov.-Dec.) 1949.
10. Garrod, L. P.: Reactions of bacteria to chemotherapeutic agents, *Brit. M. J.* **1**: 205 (Feb. 3) 1951.
11. Weinstein, L.: The spontaneous occurrence of new bacterial infections during the course of treatment with streptomycin or penicillin, *Am. J. M. Sc.* **214**: 56 (July) 1947.
12. Meads, M., Rowe, W. P., and Haslam, N. M.: Alterations in bacterial flora of the throat during oral therapy with aureomycin, *Arch. Int. Med.* **87**: 533 (April) 1951.
13. Marwin, R. M.: Relative incidence of *Candida albicans* on the skins of persons with or without skin diseases, *J. Invest. Dermat.* **12**: 229 (April) 1949.
14. Schnoor, T. G.: The occurrence of monilia in normal stools, *Am. J. Trop. Med.* **19**: 163 (March) 1939.
15. Carter, B., and Jones, C. P.: A study of the vaginal flora in the normal female, *South. M. J.* **30**: 298 (March) 1937.

16. McVay, L. V., Jr., and Sprunt, D. H.: A study of moniliasis in aureomycin therapy, *Proc. Soc. Exper. Biol. and Med.* **78**: 759 (Dec.) 1951.
17. Ravits, H. G.: Cutaneous cryptococcosis, a survey of cryptococcus on normal and pathologic skin, *J. Invest. Dermat.* **12**: 271 (May) 1949.
18. Harris, H. J.: Aureomycin and chloramphenicol in brucellosis with special reference to side effects, *J. A. M. A.* **142**: 161 (Jan. 21) 1950.
19. Williams, B., Jr.: Oral and pharyngeal complications of chloramphenicol (chloromycetin) therapy, *Am. Pract. and Digest. Treat.* **1**: 897 (Aug.) 1950.
20. Finland, M.: The present status of antibiotics in bacterial infections, *Bull. New York Acad. Med.* **27**: 199 (April) 1951.
21. Gausewitz, P. L., Jones, F. S., and Worley, G., Jr.: Fatal generalized moniliasis, *Am. J. Clin. Path.* **21**: 41 (Jan.) 1951.
22. Young, R. M., and Rettger, L. F.: Decomposition of vitamin C by bacteria, *J. Bact.* **46**: 351 (Oct.) 1943.
23. Dam, H., Glavind, J., Orla-Jensen, S., and Orla-Jensen, A. D.: Bildung von Vitamin K in Colibakterien auf synthetischem Substrat, *Naturwiss.* **29**: 287 (May) 1941.
24. Knight, B. C. J. G.: Growth factors in microbiology, *Vitamins and Hormones* **3**: 105 1945.
25. Najjar, V. A., and Barrett, R.: The synthesis of B vitamins by intestinal bacteria, *Vitamins and Hormones* **3**: 23, 1945.
26. Leitner, Z. A.: Vitamin deficiency and antibiotics, *Correspondence, Brit. M. J.* **1**: 491 (Feb. 25) 1950.
27. Black, S., Overman, R. S., Elvehjem, C. A., and Link, K. P.: The effect of sulfaguandine on rat growth and plasma prothrombin, *J. Biol. Chem.* **145**: 137 (Sept.) 1942.
28. Smith, D. T.: Nicotinic acid deficiency (pellagra), *M. Clin. North America* **27**: 379 (March) 1943.
29. Smith, D. T., and Smith, S. G.: Relation of vitamin deficiency to focal infection, *Tr. Am. Clin. and Climatol. A.* **49**, 1933.
30. Smith, D. T., and Martin, D. S.: The significance of hypersensitivity in diagnostic tests and in the therapy of infectious diseases, *North Carolina M. J.* **8**: 160 (March) 1947.
31. Smith, S. G., Smith, D. T., and Callaway, J. L.: Dysfunction of the sebaceous glands associated with pellagra, *J. Invest. Dermat.* **4**: 23 (Feb.) 1941.
32. Keefer, C. S.: Alteration of normal bacterial flora of man and secondary infections during therapy, *Am. J. Med.* **11**: 665 (Dec.) 1951.
33. Editorial: Bacterial versatility, *Ann. Int. Med.* **36**: 196 (Jan.) 1952.

## NEW DRUG THERAPIES IN ARTERIAL HYPERTENSION \*

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### INTRODUCTION

DRUGS and procedures for the treatment of essential hypertension of necessity must be nonspecific in nature, since the etiology of this disease is unknown. Undoubtedly, this fact accounts for the diverse nature of the methods that have been advocated for lowering the blood pressure and likewise for the similarity of the clinical results reported to be obtained by these various methods. Thus, surgical sympathectomy, or adrenalectomy, intravenous pyrogens, low sodium diets, the administration of adrenergic- or ganglionic-blocking agents, neural vasodilators such as veratrum, peripheral vasodilators such as nitrites, and even drugs with unknown modes of action such as nitroprusside, or *Rauwolfia serpentina*, have all been reported to be effective in lowering blood pressure in one- to two-thirds of patients, and to relieve the clinical and laboratory signs of hypertensive cardiovascular strain in one-quarter to one-half. The only common denominator in all these procedures seems to be their tendency to lower blood pressure, which lends clinical support to pathologic and experimental evidence suggesting that arterial hypertension is primarily a physiologic disturbance that eventually becomes an aggravating factor in the progress of hypertensive cardiovascular disease.

### DESIRABLE FEATURES OF HYPOTENSIVE DRUGS

Table I shows the characteristics of the drug we would like to have for the treatment of essential hypertension.

The ideal drug should be effective in lowering blood pressure continuously in a large proportion of cases. It should cause no toxic or physiologic side effects which are dangerous or even unpleasant. It should be practical for chronic use over the course of years, hence preferably should be effective by mouth and should allow adequate sleep at night.

Admittedly no agent presently available fulfills these relatively simple requirements. However, in the last five years new agents that at least are hypotensive have appeared in quantity, some of which are capable of prolonged oral use. Thus, while we are not yet in the "penicillin era" in this type of chemotherapy, perhaps we are in the "early sulfonamide-gramicidin era." Undoubtedly the next five years will see a host of new drugs tried and discarded in this field. Let us hope that at least one may be suitable for general acceptance. For until we can settle on the use of a given regimen

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TABLE I

## Desirable Features of Hypotensive Drugs

1. They should reduce the arterial pressure significantly in a large percentage of hypertensive patients.
2. They should produce no serious side effects or physiologic disturbances.
3. They should be effective by mouth and for at least eight hours.

for a five to 10 year trial we cannot acquire the data necessary really to prove whether a hypotensive agent will prolong life in patients with essential hypertension.

## CLASSIFICATION OF HYPOTENSIVE DRUGS

As shown in table 2, the hypotensive drugs may be classified into two large groups, the adrenergic-blocking or sympatholytic (denoting that their effects resemble those of a surgical sympathectomy), and the vasodilator or non-sympatholytic (denoting that they do not produce sympathectomy-like effects).

## EXAMPLES OF THE TYPES OF HYPOTENSIVE DRUGS

Of the *adrenergic-blocking or sympatholytic group* the ganglionic blockers are among the most powerful. Tetraethylammonium chloride and the longer acting pentamethonium and hexamethonium bromides are probably the most profoundly hypotensive agents in use today. The latter have been used longer and more widely in England and New Zealand than in our own country, and we must rely principally on the reports from abroad for data on their long term clinical practicability.<sup>1,2</sup> However, even in this country enough experience has been gained to give one a great respect for the methoniums and their hypotensive powers.<sup>3,4</sup>

Certainly the methonium compounds are potentially dangerous. They induce a profound fall in blood pressure, particularly in the upright posi-

TABLE II

## Types of Hypotensive Drugs

- A. Sympatholytic or Adrenergic-Blocking Agents
  - I. Ganglionic blockers
    - Examples: 1. Tetraethylammonium (T.E.A.C.)
    2. Hexamethonium (C<sub>6</sub>)
  - II. Centrally acting
    - Examples: 1. Dihydrogenated ergot alkaloids (DHO and "Hydergine")
    2. 1-Hydrazinophthalazine (Hydralazine, C-5968, or "Apresoline")
  - III. Peripherally acting
    - Example: 1. Dibenamine
- B. Vasodilator Agents
  - Examples: 1. Nitrites (peripheral)
  2. Veratrum (central neurogenic)
- C. Agents with Modes of Action As Yet Uncertain
  - Examples: 1. Thiocyanates
  2. Nitroprusside
  3. Pyrogens
  4. *Rauwolfia serpentina*

tion.<sup>3, 4, 5</sup> Perhaps any agent which would lower the blood pressure as suddenly and markedly as the ganglionic blockers might be equally dangerous. Moreover, the effect of hexamethonium in a given dose parenterally may vary markedly from patient to patient. Therefore, the dose for any one individual must be carefully determined by trial and error. By the oral route its effects are even more unpredictable. Presumably this arises from its relatively poor absorption, only about 5 per cent being absorbed from the gastrointestinal tract. Tolerance rapidly develops to the drug given parenterally or orally, so that the dosage must continually be readjusted. Finally, in addition to the dangers arising from its rather unpredictable, sudden and profound hypotensive effects, hexamethonium has other undesirable side effects, including urinary retention, abdominal discomfort, and constipation to the extent of paralytic ileus.

These facts make it necessary to give the methonium compounds with extreme caution, some workers recommending checks of the blood pressure several times daily, with dosages varied accordingly. Even with this precaution accidents have occurred. Figure 1 shows the electrocardiographic changes suggesting myocardial ischemia which developed in a patient in our clinic during a profound hypotensive response to a small parenteral dose of hexamethonium. It is interesting that the patient had no pain with this episode. Indeed, had not the electrocardiogram been continuously recorded as part of the experiment, the event might have been entirely overlooked. After recovery from the hypotension the initial changes in the electrocardiographic pattern persisted, with a clinical course typical of a myocardial infarct. Experience in our clinic with an admittedly small group of patients has impressed us with the hazards rather than the clinical benefits of this drug. We subscribe to the view expressed by Hirson and Kelsall in the *Lancet*: "Disasters are probably inevitable in the early stages of experience with any new and potent drug, but the course of hypertension is so unpredictable, particularly in women, and the response to hexamethonium bromide has been so unreliable in our experience, that we do not propose to use these drugs again except for patients in whom a relatively early death appears inevitable with any other form of medical treatment."

The *centrally acting sympatholytic or adrenergic-blocking drugs* are among the most interesting of hypotensive agents, perhaps because their mode of action is not altogether clear. Typical of this group are the dihydrogenated ergot derivatives, of which dihydroergocornine (DHO) is typical.<sup>7, 8, 9, 10</sup> This agent on acute administration causes postural hypotension, nasal congestion and bradycardia, in addition to hypotension at rest. Unfortunately, however, on prolonged administration it becomes practically inactive because of the development of tolerance by the patient.

One of the more recently described centrally acting sympatholytic drugs is hydrazinophthalazine, or C-5968.<sup>11, 12</sup> On acute administration this drug causes postural hypotension, tachycardia and frequently occipital headache, but it also may lower the resting blood pressure, particularly the dias-

tolic. The first three effects may be decreased by very gradual institution of the drug, and they tend to lessen anyway on prolonged administration, but the blood pressure lowering effect appears to persist or may even increase. It is interesting that the drug is reported to produce renal vasodilatation.<sup>13</sup>

Of the peripherally acting sympatholytic drugs, dibenamine<sup>14</sup> is the best example. It is a profoundly hypotensive drug, causing postural hypotension

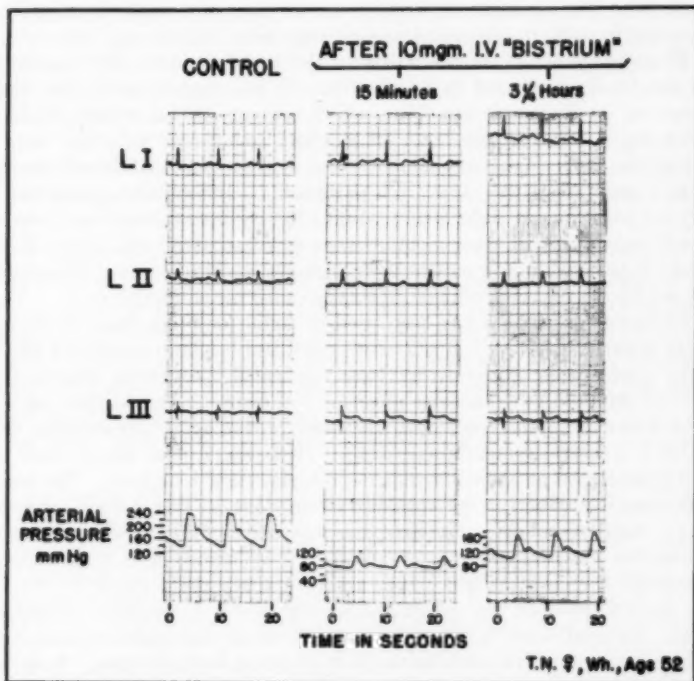


FIG. 1. Electrocardiograms (Leads I, II and III) and arterial pressure tracings (Sanborn electromanometer) in a hypertensive patient given a single slow intravenous injection of 10 mg. of hexamethonium bromide.

and bradycardia. However, it is impractical for long term use since it is given intravenously and is irritating to the veins.

Of the *non-sympatholytic drugs*, the nitrites are the oldest and chemically the simplest. They seem to cause venous as well as arterial dilatation, but are short in action, and do not seem to be clinically very effective for prolonged treatment. The veratrum derivatives<sup>7, 15, 16, 17</sup> are not sympatholytic but have a central neurogenic vasodilator effect. They are effective by mouth as well as parenterally, but can cause nausea and vomiting at a dose

very little if any higher than the hypotensive dose level. Purified derivatives or even pure alkaloids when given intravenously, do not differ significantly from the cruder preparations in this respect. For this reason most patients on continuous, chronic oral administration of veratrum experience attacks of salivation, nausea and vomiting, occasionally associated with collapse. These attacks, though unpleasant, do not appear to be dangerous, since there have been no deaths reported from them. Nevertheless, on prolonged administration the veratrum derivatives as yet have not fulfilled the promise that arose from their acute, and particularly their intravenous, use.

Thiocyanate is one of the oldest of the blood pressure lowering drugs that can be demonstrated to be effective. It has largely fallen into disuse because of its toxic side reactions, which require careful control by blood level assay. Nitroprusside,<sup>18</sup> which has had limited trial recently, may act through the thiocyanate mechanism, since it gives a similar blood chemical reaction and causes the same toxic symptoms. Intravenous pyrogens<sup>18, 19</sup> daily for from five to eight weeks admittedly are heroic, and have been advocated only when all other methods have failed to arrest the course of malignant hypertension in a patient with adequate renal function. Presumably they act by causing general and especially renal vasodilatation.

*Rauwolfia serpentina* has been used in India for more than 10 years to relieve hypertension.<sup>20, 21</sup> It is a native plant and has been given as a powder of the crude root. Recently we have confirmed the clinical reports from India on the mildly hypotensive effect of this drug.<sup>22</sup> In addition, we have found it to cause nasal congestion and bradycardia, actions resembling those of DHO, a central sympatholytic drug. However, it does not produce postural hypotension or abolish sympathetic vasopressor reactions. The bradycardia that it produces is not abolished by atropine, so that it does not appear to be a vagal stimulant. The drug has a sedative effect, which may require a reduction or an interruption of dosage. It apparently also has a tendency to promote a gain in weight. It is a slowly acting drug, requiring three to four days to produce any effect and several weeks to produce its maximal effect. In small doses it is well tolerated by most hypertensive patients and reduces the arterial pressure moderately in about half of them. It is most satisfactory alone in persons with anxiety neurosis and a labile blood pressure, particularly when associated with tachycardia. It has little or no blood pressure lowering effect when given alone in chronic, severe, fixed hypertension, although it is bradycrotic and sedative and may result in subjective improvement. It finds its best use in combination with other hypotensive drugs, particularly hydrazinophthalazine and veratrum, which may be easily added to the regimen, if necessary.

#### COMBINATIONS OF DRUGS

Since it seems likely that none of the various hypotensive drugs is wholly specific against the causes of essential hypertension, it has appeared appropriate to use combinations of them in the more resistant cases. There seems

little question that hypotensive drugs and, for that matter, sympathectomy and dietary treatment, are more effective in combination than alone. Thus, sodium restriction in the same patient appears definitely more effective after sympathectomy than before.<sup>23</sup> The same is true of drugs after sympathectomy as compared with before.

Likewise, various combinations of drugs have been uniformly reported as more effective than any one alone. Particular attention has been called recently to the combined use of hexamethonium and hydrazinophthalazine.<sup>3, 4</sup> However, it may be emphasized that the dangers of these two drugs in combination are, if anything, greater than of either one alone. It would appear to us that the dangers are much too great to allow these two drugs to be used together except in the most desperate of cases and under the most carefully controlled experimental conditions.

In our clinic we have relied chiefly upon various combinations of hydrazinophthalazine, Rauwolfia and veratrum, principally because these drugs appear to be the safest, both when used alone or in combination, of any medicinal regimen we have tried. If instituted gradually they may be given safely in ambulatory patients, with only weekly or even monthly checks of blood pressure. As a matter of fact, because they can be used together in relatively small doses, these drugs in combination may produce a greater hypotensive action with fewer symptoms or side effects than can be produced by any one of them alone. They are all effective orally, they may be given in a four dose schedule, and they all appear to be active and well tolerated certainly for many months.

Three case histories will serve to illustrate these points.

#### CASE REPORTS

*Case 1.* A 30 year old white male was born with a spina bifida and meningocele which, though operated upon in infancy, left him paraplegic and unable to control the vesical and rectal sphincters. Since childhood he had suffered numerous attacks of pyelonephritis, and had developed a constant anxiety state over the physical and social consequences of his misfortunes. Five years ago he had had a nervous breakdown. In spite of all these difficulties, he fought his way along in the world, married and became gainfully employed. Since the age of 17 he had known of rises in blood pressure, but only for one year had he complained of severe headaches and palpitation. When first seen in our clinic his blood pressure was 200/150 mm. of Hg, and pulse 120. Non-protein nitrogen was normal, but phenolsulfonphthalein excretion was reduced to 54 per cent in two hours. The cold pressor test produced a rise in blood pressure to 230/180 mm. of Hg, and the sodium amylal test a fall to 140/100 mm. of Hg. Electrocardiogram showed left ventricular strain (figure 2).

When the patient was given placebos for one week no beneficial effects were observed. On separate trial doses, Rauwolfia and veratrum were well tolerated but hydrazinophthalazine was not. He was then given three tablets of Rauwolfia ("Serpina") a day for six weeks and his pressure leveled off at 175/105 mm. of Hg and his pulse at 80. He was enthusiastic about his subjective improvement, particularly the striking relief of headache and palpitation. He was then continued on Rauwolfia, with veratrum added in small oral doses. After four weeks, and for the ensuing 16

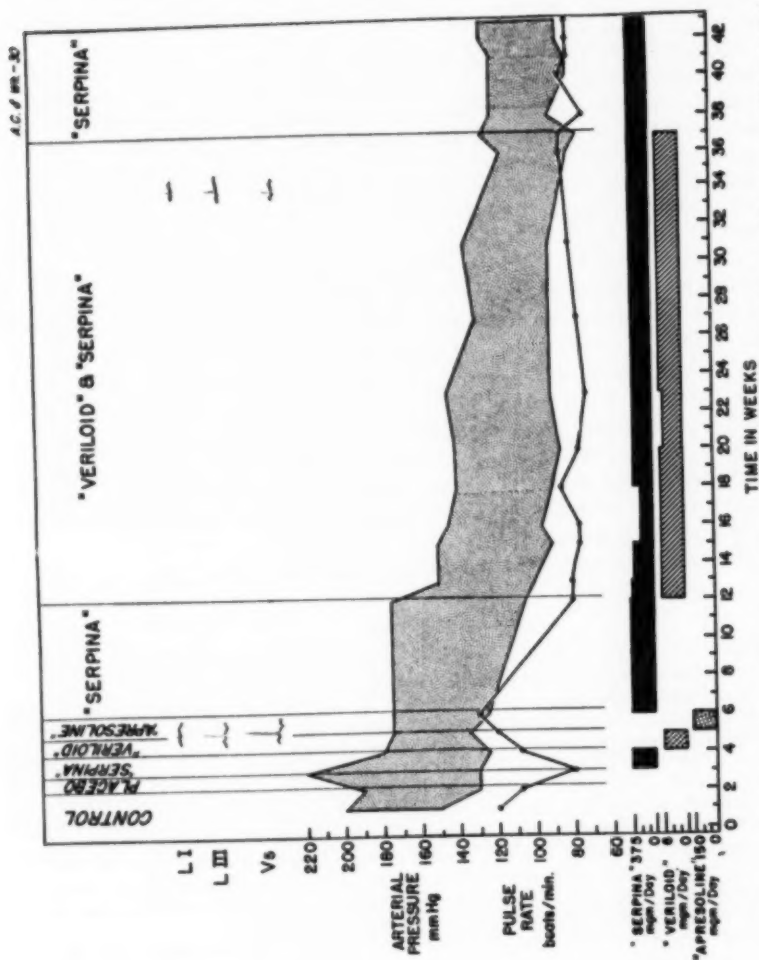


Fig. 2. Chart showing oral medication, electrocardiograms (Leads I, III and V<sub>6</sub>), arterial pressure, pulse rate and dosages in a hypertensive patient (case 1) treated medically.

weeks, his pressure was steadily around 140/90 mm. of Hg and pulse rate 80. He gained 15 pounds in weight. At this point he developed a severe anxiety attack over his work, being unable to keep from trembling with a "nameless fear." He was admitted to the hospital and his blood pressure of 140/100 mm. of Hg fell on sodium amytal test to 100/70 mm. of Hg. Renal function was unchanged but the electrocardiogram was now within normal limits. After two days he was discharged on the same medication, was given psychotherapy, and slowly improved. The blood pressure continued to moderate to 125/75 mm. of Hg. At this point veratrum was discontinued, but Rauwolfia was maintained. The blood pressure has remained normal for the past six weeks.

This patient represents a severe but labile hypertensive with some renal impairment due to pyelonephritis who has shown a striking response to Rauwolfia supplemented by veratrum.

*Case 2.* A 43 year old housewife had had high blood pressure during her first pregnancy at the age of 20. During the intervening years she had been told at various times that her pressure was elevated, but had had no symptoms until two years prior to coming to our clinic, when she began to complain of easy fatigability and nosebleeds. Her blood pressure was 230/140 mm. of Hg, pulse 84. The heart was enlarged to the left, but renal function was normal. The eyegrounds showed Grade II-III hypertensive changes (figure 3).

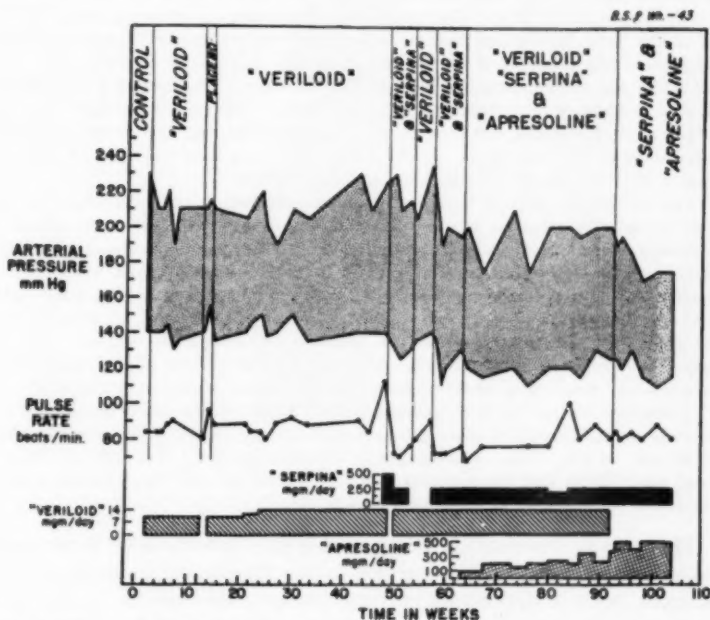


FIG. 3. Chart showing oral medication, arterial pressure, pulse rate and dosages in a hypertensive patient (case 2) treated medically.

She was placed on veratrum, which produced little or no lowering of resting blood pressure as compared with placebo treatment. However, subjectively she felt somewhat better on veratrum than on placebos, so was continued on the drug. After 11 months she was given Rauwolfia in addition to veratrum. This seemed to cause a slight but definite lowering of blood pressure, which disappeared when this drug was stopped and veratrum alone was continued. The two drugs were therefore continued together, and after five weeks the blood pressure leveled off at about 200/130 mm. of Hg.

Hydrazinophthalazine was then instituted in small doses without producing symptoms. Initially there seemed to be a further small drop in pressure, but since it was not sustained the dosage of hydrazinophthalazine was increased. Rauwolfia was continued but veratrum was stopped. Over the course of the past three months, and in spite of a very trying emotional disturbance, the blood pressure has moderated further to about 175/115 mm. of Hg. The patient is completely asymptomatic.

This patient represents a fairly severe fixed type of hypertensive who does not respond to oral veratrum, but does now appear to be moderating on hydrazinophthalazine and Rauwolfia.

*Case 3.* A 22 year old college student had been found to have hypertension one year prior to admission when checked for an Air Force commission. He felt well, however, except for mild dyspnea, until about four months prior to admission, when he noticed easy fatigability. The resting blood pressure on admission was 180/110 mm. of Hg, pulse 80. Renal function was normal and electrocardiogram borderline. Cold pressor test produced a rise in blood pressure to 235/145, the Valsalva a rise to 215/130, and sodium amyltal a fall to 130/95. He was discharged on no therapy and was re-admitted for check-up six months later. The blood pressure then was 180/120 mm. of Hg and renal function was still normal, but the electrocardiogram showed definite left ventricular strain. The cold pressor response was 230/140, the Valsalva 245/150, and the sodium amyltal 150/100 (figure 4).

The patient was started on hydrazinophthalazine, which had little effect initially except to cause tachycardia, postural hypotension and headache. He was faithful to the therapy, but after six weeks his resting blood pressure had moderated only to about 170/110 mm. of Hg, with a pulse averaging 110. He was then given small doses of veratrum in addition to the hydrazinophthalazine, with apparently only slight additional effects on blood pressure but a definite slowing of pulse rate, which now averaged about 80. Electrocardiogram still showed left ventricular strain. After six weeks on this regimen Rauwolfia was added, and over the course of two months there was a gradual lowering of blood pressure to 135/80 mm. of Hg and pulse to 75.

Thereafter, except for one reading of 140/70 mm. of Hg when the patient was extremely upset, the resting blood pressure was normal, indeed, a low normal—about 110/60 mm. of Hg. The electrocardiogram became normal. The cold pressor response was 145/90, and the Valsalva 125/70. Veratrum was then omitted, and for three weeks the pressure has remained normal.

This patient represents a young, moderately severe, labile hypertensive who developed adverse electrocardiographic changes on six months of no treatment, with disappearance of these changes after return of the blood pressure to normal on hydrazinophthalazine supplemented by veratrum and Rauwolfia.

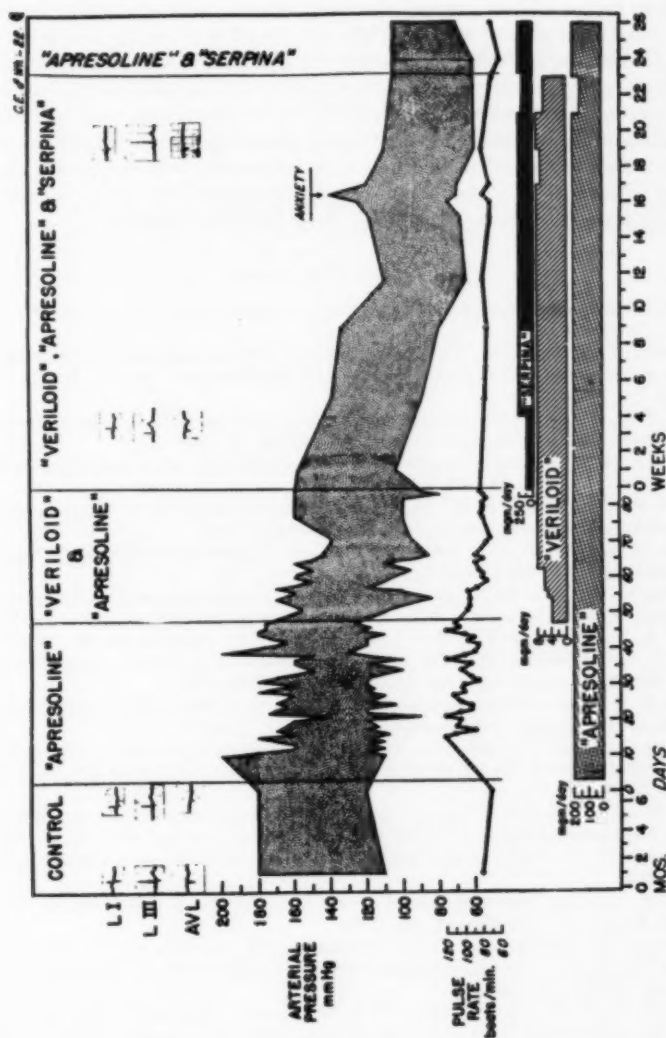


FIG. 4. Chart showing oral medication, electrocardiograms (Leads I, III and aVL), arterial pressure, pulse rate and dosages in a hypertensive patient (case 3) treated medically. Note the changes in time scale.

## SUMMARY AND CONCLUSIONS

Various types of blood-pressure-lowering drugs are now becoming available for long term clinical trial. While no one of these is as yet ideal, a number of them are effective in lowering blood pressure in hypertensive patients, particularly when used in combination. Combinations of hydrazinophthalazine, veratrum and Rauwolfia appear to be safe and well tolerated when given orally in relatively small doses over long periods of time, and usually produce a gradual moderation of hypertension, with subjective and objective improvement. Only very long term studies will prove whether such medical regimens prolong the lives of hypertensive patients.

## BIBLIOGRAPHY

1. Report of the Royal Society of Medicine. Medical treatment of hypertension, *Lancet* **1**: 492 (March 8) 1952.
2. Kilpatrick, J. A., and Smirk, F. H.: Comparison of oral and subcutaneous administration of methonium salts in the treatment of high blood-pressure, *Lancet* **1**: 8 (Jan. 5) 1952.
3. Freis, E. D., Finnerty, F. A., Jr., Schnaper, H. W., and Johnson, R. L.: The treatment of hypertension with hexamethonium, *Circulation* **5**: 20, 1952.
4. Schroeder, H. A.: Control of hypertension by hexamethonium and 1-hydrazinophthalazine, *Arch. Int. Med.* **89**: 523, 1952.
5. Restall, P. A., and Smirk, F. H.: Regulation of blood pressure levels by hexamethonium bromide and mechanical devices, *Brit. Heart J.* **14**: 1, 1952.
6. Hirson, C., and Kelsall, A. R.: Letters to the Editor. Methonium compounds in hypertension, *Lancet* **1**: 585 (March 10) 1951.
7. Wilkins, R. W., Freis, E. D., and Stanton, J. R.: Essential hypertension. Laboratory studies in human beings with drugs recently introduced, *J. A. M. A.* **140**: 261, 1949.
8. Freis, E. D., Stanton, J. R., Litter, J., Culbertson, J. W., Halperin, M. H., Moister, F. C., and Wilkins, R. W.: The hemodynamic effects of hypotensive drugs in man. II. Dihydroergocornine, *J. Clin. Investigation* **28**: 1387, 1949.
9. Goetz, R. H.: The effect of sympathicolytic drugs on the cardiovascular system in man with special reference to hypertension, *Angiology* **2**: 1, 1951.
10. Barcroft, H., Konzett, H., and Swan, H. J. C.: Observations on the action of the hydro-genated alkaloids of the ergotoxine group on the circulation in man, *J. Physiol.* **112**: 273, 1951.
11. Freis, E. D., and Finnerty, F. A., Jr.: Suppression of vasomotor reflexes in man following 1-hydrazinophthalazine (C-5968), *Proc. Soc. Exper. Biol. and Med.* **75**: 23, 1950.
12. Schroeder, H. A.: The effect of 1-hydrazinophthalazine in hypertension, *Circulation* **5**: 28, 1952.
13. Reubi, F. C.: Renal hyperemia induced in man by a new phthalazine derivative, *Proc. Soc. Exper. Biol. and Med.* **73**: 102, 1950.
14. Nickerson, M., and Goodman, L. D.: Pharmacological properties of new adrenergic blocking agent: N, N-dibenzyl- $\beta$ -chloroethylamine (dibenamamine), *J. Pharmacol. and Exper. Therap.* **89**: 167, 1947.
15. Freis, E. D., Stanton, J. R., Culbertson, J. W., Litter, J., Halperin, M. H., Burnett, C. H., and Wilkins, R. W.: The hemodynamic effect of hypotensive drugs in man. I. Veratrum viride, *J. Clin. Investigation* **28**: 353, 1949.
16. Wilkins, R. W.: Veratrum viride and essential hypertension, *New England J. Med.* **242**: 535, 1950.

17. Wilkins, R. W.: Veratrum viride in hypertensive cardiovascular disease, Mod. Concepts Cardiovas. Dis. **20**: 89 (Feb.) 1951.
18. Page, I. H.: Treatment of essential and malignant hypertension, J. A. M. A. **147**: 1311, 1951.
19. Page, I. H.: Pyrogens in the treatment of malignant hypertension, Mod. Concepts Cardiovas. Dis. **18**: 51, 1949.
20. Bhattia, B. B.: On the use of *Rawwolfia serpentina* in high blood pressure, J. Indian M. A. **11**: 262, 1942.
21. Vakil, R. J.: A clinical trial of *Rawwolfia serpentina* in essential hypertension, Brit. Heart J. **11**: 350, 1949.
22. Wilkins, R. W., Judson, W. E., and Stanton, J. R.: Preliminary observations on *Rawwolfia serpentina* in hypertensive patients, presented before the New England Cardiovascular Society on February 4, 1952. Proceedings of the New England Cardiovascular Society, 1951-1952, page 34.
23. Kinsey, D.: Personal communication.

## THE INCIDENCE AND ETIOLOGIC BACKGROUND OF CHRONIC BIOLOGIC FALSE-POSITIVE REACTIONS IN SEROLOGIC TESTS FOR SYPHILIS: PRELIMINARY REPORT\*

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PRESENT standard serologic tests for syphilis (hereafter abbreviated STS), routinely discovered in patients who have no history or physical evidence of that infection, may represent either latent syphilis, acquired or congenital, or biologic false-positive reactions (hereafter abbreviated BFP).

BFP reactors may be divided into two categories, acute and chronic.<sup>1</sup> The acute reactions are due to a large number of infections, bacterial, viral, plasmodial, rickettsial or protozoal. They appear during or immediately after such a precipitating infectious cause, and regress spontaneously to normality within a brief period, not exceeding six months.

Chronic BFP reactors, on the other hand, are characterized by the usual absence of any of the commonly known precipitating causes of acute BFP reactions, and by the fact that the false-positive STS, instead of disappearing spontaneously, persists over a period of years, perhaps for a lifetime.

This paper is concerned in preliminary fashion with the identification of the chronic BFP reactor by the use of the treponemal immobilization test, with the incidence of such reactions in a particular population group, and with some observations as to the etiologic background, so far poorly defined, of this type of serologic abnormality.

### THE TREPONEMAL IMMOBILIZATION TEST IN IDENTIFICATION OF THE CHRONIC BIOLOGIC FALSE-POSITIVE REACTOR

The existence of a treponemal immobilizing (hereafter abbreviated TPI) antibody in syphilis and other treponematoses and its separate identity from reagin have been demonstrated by Nelson and Mayer.<sup>2</sup> Published studies indicate that the TPI antibody does not occur in normal persons or in non-syphilitic diseases, but does appear with regularity in persons with untreated syphilis and related treponematoses. The behavior of the TPI antibody within the first year or two after treatment of persons with early or late syphilis has likewise been reported.<sup>1</sup> This antibody commonly disappears early from the serum of persons with treated early syphilis, as does reagin, but at a slower rate and not necessarily in parallel. In treated late syphilis,

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on the other hand, the TPI antibody usually does not disappear from the serum within the first two years following treatment.

To establish the validity of the TPI test in the differentiation of syphilis from BFP reactions, it is essential to study the behavior of the antibody over a long period of time following treatment. For this purpose we have utilized patients from private practice in whom the original diagnosis of symptomatic syphilis, early or late, had been confirmed, and to whom treatment for syphilis had been given at intervals ranging for from one to 40 years before the performance of the TPI test.

TABLE I  
The TPI Test in Treated Early Syphilis

Number of Patients	TPI Test		
	Positive	Doubtful	Negative
31	8* (29%)	1	22** (71%)

\* Of these, 4 seronegative with standard STS.

\*\* Of these, 3 seropositive with standard STS.

In table 1 are shown 31 patients in whom the diagnosis of early syphilis was originally confirmed by the dark-field demonstration of *Treponema pallidum*. These patients had been treated (for the most part with metal chemotherapy, a few with penicillin) from one to 35 or more years ago, the TPI test having been performed after this long interval. Of the 31 patients, nine (29 per cent) were positive or doubtful with the TPI test; 22 (71 per cent) were negative. As the table indicates, TPI test results did not necessarily parallel those with standard serologic tests, since of the nine positive reactors with the TPI test, four were STS-negative, while of the 22 negative TPI reactors, three were STS-positive with standard technics.

TABLE II  
The TPI Test in Treated Late Syphilis\*

Number of Patients	TPI Test		
	Positive	Doubtful	Negative
256	246 (97.3%)**	3	7 (2.7%)***

\* In all patients, diagnosis based on definite clinical evidence and/or abnormal C.S.F.

\*\* Of these, 33 seronegative with standard STS.

\*\*\* Of these, 3 seropositive with standard STS.

In contrast to these data are the results in 256 patients with symptomatic late syphilis, presented in table 2. In these patients the original diagnosis of syphilis was in every instance made on the basis of evidence other than the mere presence of a positive standard blood STS. The majority had obvious clinical evidence of syphilis, including benign late gummatous lesions, cardiovascular syphilis or neurosyphilis. A few had asymptomatic neurosyphilis. A few others, diagnosed as latent syphilis, were the mothers of

congenitally syphilitic children. All had also been treated for syphilis, by one or another means, at intervals of from one to 40 years before the performance of the TPI test. In them, the TPI test was positive or doubtful in 249 (97.3 per cent) and negative in only seven (2.7 per cent). Again, there is lack of parallelism of the TPI test with the standard STS.

These data indicate that while the TPI antibody usually disappears from the serum of persons with treated early syphilis, it rarely disappears in persons whose original treatment was for late syphilis: instead, it persists for a lifetime.

The interpretation which may be put on various combinations of standard STS and TPI test results is indicated in table 3. A patient who is negative with both tests may be assumed either to be normal (so far as syphilis and BFP reactions are concerned) or, alternately, to have had treated early syphilis. One who is positive with both tests has syphilis, treated or untreated. The combination, negative with standard tests, positive with the TPI test, also means syphilis. The combination, TPI test negative, stand-

TABLE III  
Serologic Patterns

Reagin	T.I. Antibody	Interpretation
0	0	Normal; treated early syphilis
+	+	Syphilis
0	+	Treated late syphilis (usually)
+	0	BFP (usually); treated early syphilis (rarely)

ard STS positive, is a practically certain indication of biologic false-positivity.

#### THE INCIDENCE OF CHRONIC BFP REACTORS

Published data as to the incidence of BFP reactions, acute or chronic, in various nonsyphilitic diseases are highly misleading, since they provide only the incidence of positive standard tests. Except in the case of leprosy,<sup>3</sup> such results have not been checked by the TPI test. In all reported series, therefore, the positive reactors with standard technics include some persons with syphilis as well as some BFP reactors.

We have approached the problem of incidence of chronic BFP reactions by a study of private patients referred to us in consultation for the elucidation of routinely discovered positive STS in the absence of any clinical evidence of syphilis. These are persons of both sexes who, until a few years ago, would usually have been diagnosed as latent syphilis and treated as such. Private patients have been selected because they are white (thereby eliminating confusion caused by the high incidence of syphilis in the Negro race); of a relatively high socio-economic level (i.e., from a population group in which the incidence of syphilis is known to be low); and of superior intelligence, able to give reliable histories, and willing to coöperate in detailed examination and in long-term follow-up. Our present material includes 300

such persons, all of whom have been examined for history and physical and epidemiologic evidence of syphilis, and all subjected to the TPI test. In this group (table 4) 54 per cent have been identified as latent syphilis on the basis of positive TPI tests, and 46 per cent as BFP reactors.

Nelson is currently presenting data concerning parallel TPI and standard STS in U. S. Navy personnel routinely discovered to be standard STS-positive.<sup>4</sup> In his material (consisting mostly of young males), the incidence of BFP reactions, as indicated by negative TPI tests, is about 35 per cent.

These two series of patients are a strong indication that in certain population groups, nearly half of the positive standard STS discovered in routine blood testing do not represent syphilis, but do instead represent BFP reactions.

#### THE ETIOLOGIC BACKGROUND OF CHRONIC BFP REACTORS

Little is so far known of the etiologic background of chronic BFP reactions. The only identified infection is leprosy, in which the incidence of BFP reactions is variously reported to be from 40 to 60 per cent. This disease is not the cause of any of the chronic BFP reactions in our series.

The only other chronic disease so far suggested as a frequent cause of

TABLE IV  
The Incidence of Chronic BFP Reactors vs. Latent Syphilis

Number of Patients Seropositive with Standard STS	TPI Test	
	Positive (Latent Syphilis)	Negative (BFP) Reactors
300	164 (54.7%)	136 (45.3%)

biologic false positivity is lupus erythematosus, discoid or disseminated. The incidence of BFP reactions reported in various series of patients with this disease ranges from 5 to 30 per cent or more; but, as we have pointed out, these data are unreliable since they do not take into consideration the number of persons with lupus who also have syphilis, particularly as verified by the TPI test.

As yet, neither we nor others have attempted to identify the incidence of chronic BFP reactors in particular disease conditions by means of the performance of parallel standard and TPI tests. Instead, we have approached the problem in another manner.

We have restudied patients identified as chronic BFP reactors by complete medical survey, planned to be periodically repeated over a period of years. Special attention is devoted to anamnestic points often not previously recorded, to detailed physical examination, and to a laboratory routine which includes complete hemogram, urine studies, total blood protein, A/G ratio, cephalin flocculation and thymol turbidity tests (and other liver function tests when these are positive), a search for L.E. cells in the peripheral blood, and other laboratory and x-ray examinations as indicated.

Of the 136 BFP reactors so far identified in our patient material, 51 have completed at least one detailed reexamination. Table 5 indicates that, of these 51, some significant abnormality other than the BFP reaction has been discovered in all but six.

Five patients have proved collagen disease (disseminated lupus erythematosus in four, rheumatoid arthritis in one). One patient each has sarcoid,

TABLE V  
The Etiologic Background of Chronic BFP Reactors

Number of Patients	Definite Diagnosis		Probable Diagnosis		Clinically Normal, but Distinctive Laboratory Pattern	Normal Except BFP
	Collagen Disease	Other	Collagen Disease	Other		
51	5 (15.7%)	3*	21 (45.1%)	2**	14 (27.4%)	6 (11.7%)

\* Sarcoid, Hodgkin's and Gaucher's disease, 1 each.

\*\* Sarcoid in both.

Hodgkin's disease and Gaucher's disease. In 21 others there is history or physical evidence which raises strong suspicion of one of the group of collagen diseases (disseminated lupus, rheumatoid arthritis, periarteritis nodosa or rheumatic fever), though in none has the diagnosis yet been firmly established. Two other patients are suspected of sarcoid, which also is not yet proved. Practically all of the 23 patients in this group of "suspects" likewise present a distinctive pattern of laboratory changes other than the BFP reaction.

TABLE VI  
Typical Laboratory Abnormalities in Chronic BFP Reactors

TPI Test	0
Standard STS	+ (Variable titer)
Sedimentation Rate	Persistently elevated
Cephalin Flocculation	++ to ++++
Thymol Turbidity	Normal to weakly +
B.S.P.	0
Other Evidence Liver Disease	0
Serum Globulin	Sometimes elevated
Urine	Sometimes proteinuria and cylindruria
Renal Function	Otherwise normal
L. E. Cells	See text

The typical laboratory abnormalities found in these 23 suspects, and in 14 other patients who are clinically normal, are detailed in table 6. The confirmed positive standard STS is present for one or more years, and is usually but not necessarily of low titer. The sedimentation rate in most has been known to be persistently elevated for years, without other obvious cause. The cephalin flocculation test is moderately to strongly positive in most, with the thymol turbidity test normal to weakly positive. These two

abnormalities cannot be interpreted as evidence of liver disease, since persons who show them have otherwise normal liver function tests (particularly bromsulphalein excretion) and are without other clinical or laboratory evidence of involvement of the liver. These abnormalities are to be interpreted, as they have been by others, as a quantitative, perhaps also qualitative, expression of some abnormality in the blood proteins, particularly globulins.<sup>5</sup> The serum globulin is sometimes elevated with a shift in the A/G ratio. The urine sometimes shows proteinuria and cylindruria, but these patients are without hypertension or other evidence of damage to renal function. Except in those patients with clinically characteristic disseminated lupus erythematosus, LE. cells have not been found in the circulating blood.

These laboratory abnormalities, which have appeared in 37 of our 51 chronic BFP reactors, are likewise those commonly found in persons with actual clinical evidence of collagen disease, usually disseminated lupus.

In only six patients in our entire group of 51 so far examined have no clinical or laboratory abnormalities other than the BFP reaction been found.

#### SUMMARY

These data suggest that:

1. The chronic BFP phenomenon is far from innocuous, as has heretofore been thought.
2. It is often related to and may be the first evidence of serious underlying disease.
3. Collagen disease may be closely related to the chronic BFP phenomenon.
4. If these observations are borne out by further study, an opportunity may be provided better to define the early manifestations and natural history of the collagen disease group.

#### BIBLIOGRAPHY

1. Moore, J. E., and Mohr, C. F.: The classification, recognition, incidence, and etiologic background of biologic false positive serologic tests. Preliminary report, *J. A. M. A.* **150**: 467, 1952.
2. Nelson, R. A., and Mayer, M. M.: Immobilization of *T. pallidum* in vitro by antibody produced in syphilitic infection, *J. Exper. Med.* **89**: 369, 1949.
3. Nelson, R. A., Zheutlin, H. E. C., Austin, P. G. M., and Hill, J. H.: Application of treponemal immobilization test to problems of clinical syphilis. Presented at the Symposium on the Later Advances in the Study of the Venereal Diseases, Washington, D. C., April 28, 1950.
4. Nelson, R. A.: Treponemal immobilization test program in the United States Navy. Presented at the Symposium on Recent Advances in the Study of Venereal Diseases, Washington, D. C., May 2, 1952.
5. MacLagan, N. F., Martin, N. H., and Lunnon, J. B.: The mechanism and interrelationships of the flocculation tests, *J. Clin. Path.* **5**: 1, 1952.

## THE RATIO BETWEEN PHOSPHOLIPID AND THE CHOLESTEROLS IN PLASMA AS AN INDEX OF HUMAN ATHEROSCLEROSIS\*

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ATHEROSCLEROSIS has come to be recognized as a disease which is not an inevitable result of vascular aging, but rather an episodic process which may be to some extent reversible. Because of this, there have been many attempts to identify measurable abnormalities which could be employed to detect this tendency in its earliest stages.<sup>1-15</sup> One of the most recent of these is the ratio between phospholipid and total cholesterol in the blood serum. The evidence in favor of this ratio as the circulating symbol of atherosclerosis might be summed up as follows:

There is a decrease in the ratio, phospholipid over total cholesterol, in the blood of cholesterol-fed rabbits<sup>16</sup> and of thiouracil-treated, cholesterol-fed dogs<sup>17</sup> as compared with normal animals. These régimes are well known methods of producing atherosclerosis in the laboratory. However, when cholesterol-fed rabbits are also treated with intravenous detergents, the ratio remains normal and atherosclerosis is markedly inhibited.<sup>16</sup> In man, similar changes in this ratio have been demonstrated in nephrosis, hypothyroidism and essential xanthomatosis, all of which are known to predispose to atheromatous disease.<sup>18</sup> Contrasting these observations with their experience in primary xanthomatous biliary cirrhosis, where the high cholesterol sera have phospholipid-total cholesterol ratios greater than normal, Ahrens and Kunkel<sup>18</sup> were led to suggest, in 1949, that a relationship exists between the fixation of lipid in intimal cells and decreased phospholipid-cholesterol ratios. Though their reported experience with atheromatous disease in xanthomatous biliary cirrhosis is not completely borne out by the observations of others,<sup>19</sup> the following year brought further evidence which appeared to support their suggestion concerning this ratio and atheromatosis. Morri-son and his colleagues<sup>20</sup> and Gertler and Garn<sup>21</sup> reported lower average phospholipid-total cholesterol ratios in patients who had sustained myocardial infarctions than in a group of apparently normal subjects.

The weight of this evidence is, of course, considerable. Yet, on closer scrutiny, it is found to be based on somewhat hazardous logic, i.e., that the laboratory situation mimics the spontaneous disease in man, that coincidence of atherosclerosis and this abnormal ratio implies a causal connection, and

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that the abnormal ratio found in certain diseases is meaningful in itself, having no alternative explanation.

We proposed, therefore, to test this concept further, and to that end drew up the following six questions:

1. Do the two substances being related exist biologically?
2. Is there a demonstrable relationship between them?
3. How is this relationship altered in diseases which are the manifestation of atherosclerotic vascular changes?
4. How is this relationship altered in diseases which predispose to the development of atherosclerosis?
5. Are there diseases which show this same abnormality but are not associated with an abnormal degree of atherosclerosis?
6. Is there any other explanation for these alterations which have been observed?

The answers to these questions should define the value of the phospholipid-cholesterol ratio as an index of atherosclerosis.

*1. Do the two substances being related exist biologically?*

Whether these two substances exist as such in the serum is most easily answered in the biochemical laboratory where they are determined. Phospholipid is determined as milligrams of phosphorus contained in the lipids,<sup>22, 23</sup> following which this "lipid phosphorus" value may be multiplied by a factor of 25, being thus converted to milligrams of lecithin. Since lecithin is the predominant phosphorus-containing lipid in serum, and is also the one responsible for most of the change when abnormal values are found,<sup>24, 25</sup> we can accept this value as representative, at least, of something which actually is present.

With cholesterol, however, the story is somewhat different. It is well known that cholesterol exists in the blood stream, not as a single substance which can be totaled, but in two chemical forms, in one being esterified with fatty acids, and in the other, as free cholesterol. The "total cholesterol" of the chemist, therefore, bears about the same relationship to the biological facts of life as does his "total serum proteins." Already, then, this ratio we are considering becomes suspect, in that one of its components has no physiologic counterpart.

*2. Is there a demonstrable relationship between them?*

Further evidence against the validity of this ratio can be found in the studies which we first reported in preliminary form in March, 1950,<sup>26</sup> and which were presented in greater detail in November. Independent confirmation of the essential features of this report was furnished in the paper of Albrink, Man and Peters of that year.<sup>27</sup> In an attempt to define the relationship between the phospholipids and the the cholesterol in human plasma, we selected 242 determinations from normal subjects and from patients with a variety of disease states, as shown in table 1. By using such a miscellaneous group, we hoped to eliminate the effect of any given disease on these

substances and at the same time to secure the maximal variation of their values.

Figure 1A shows our results when phospholipids were plotted against total-cholesterols. These were in accord with the earlier work of Man, Peters, and their colleagues,<sup>28-32</sup> in that most of the values fell along a curve but certain ones showed marked dissociation. These latter were found to be those patients with liver disease who manifested the relative increase in free cholesterol which may occur with severe liver damage. Patients with liver disease whose free cholesterol formed the normal proportion of the total, regardless of its absolute value, showed no such dissociation.

However, when free cholesterol is substituted for total cholesterol, as shown in figure 1B, we see a much more tightly knit curve, and the formerly dissociated liver cases have been brought into line. Since these values represent not only normal subjects but also a wide variety of disease states, we were able to conclude that a relationship does exist between phospholipid and free cholesterol, that this relationship is independent of disease process, and that no such relationship exists between phospholipid and total cholesterol.

TABLE I

Diagnostic Group	No. Determinations
1. Controls (normals)	102
2. Essential familial hypercholesteremia	49
3. Liver disease	31
4. Hypothyroidism	20
5. Nephrotic stage of nephritis	4
6. Essential hypertension	11
7. Diabetes mellitus	3
8. Coronary artery disease	3
9. Combinations of 2 through 8	19

The observations of Kendall<sup>17</sup> and of Kellner<sup>18</sup> that, in experimental cholesterol atherosclerosis, there was a progressive, relative phospholipid deficiency as the circulating cholesterol rose, led us to examine our data to see whether hypercholesteremic man exhibited this same phenomenon. In figure 2A we can see whether the phospholipids keep pace with the free cholesterol rise in human hypercholesteremia. If they do, then the ratio, phospholipid over free cholesterol, should remain constant, and a straight line paralleling the free cholesterol axis would be obtained. Instead, with a rising free cholesterol, there is a progressive diminution in this ratio until its value approaches 2.00, following which it remains constant. When this limiting ratio of milligrams is converted into a molar ratio, it is found to define a state where there exists in the plasma one molecule of phospholipid for each molecule of free cholesterol. Apparently, then, the body will not tolerate less phospholipid than this. The data of Albrink, Man and Peters,<sup>27</sup> when treated in the same way, show a similar limiting value.

The next step was to try to define mathematically this relationship between free cholesterol and phospholipid. We were impressed, as were Al-

brink and her colleagues, by the apparent tendency of the data at the lower end of the curve of figure 1B to deviate away from the axis of an imaginary straight line through the values above. It was found that, by plotting these values on logarithmic axes, this portion could be straightened out, as shown in figure 2B. The equation seen in this figure was calculated by the method

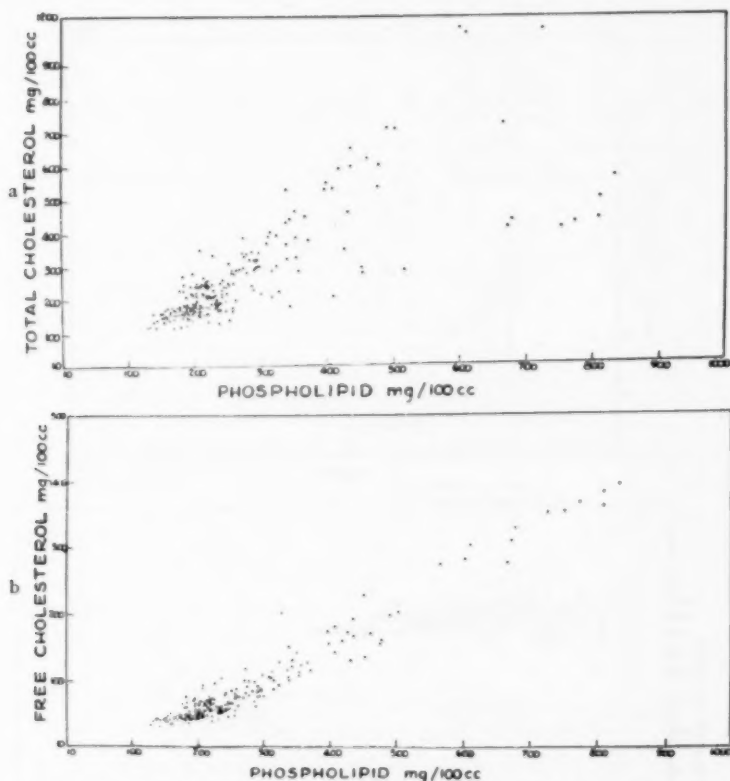


FIG. 1A. (upper) The inconsistent relationship between total cholesterol and phospholipid as contrasted with B. (lower) The constant relationship between free cholesterol and phospholipid.

of least squares, and a test of the agreement of the data with this straight line yielded a correlation coefficient of 0.945. This means that the chance that this is not a straight-line function is far less than 1 in 100. Though we have reason to suspect, despite this extraordinary correlation coefficient, that this may not be the best mathematical definition of this relationship, it is suffi-

ciently good to allow the testing of various disease states individually, to see whether they present significant deviations from the group as a whole.

Figure 3 shows the method of testing we have employed. In the upper left graph, the data from our apparently normal subjects are recorded. The solid line expresses the relationship found for the whole series. On either side, broken lines are drawn at a distance corresponding to two standard

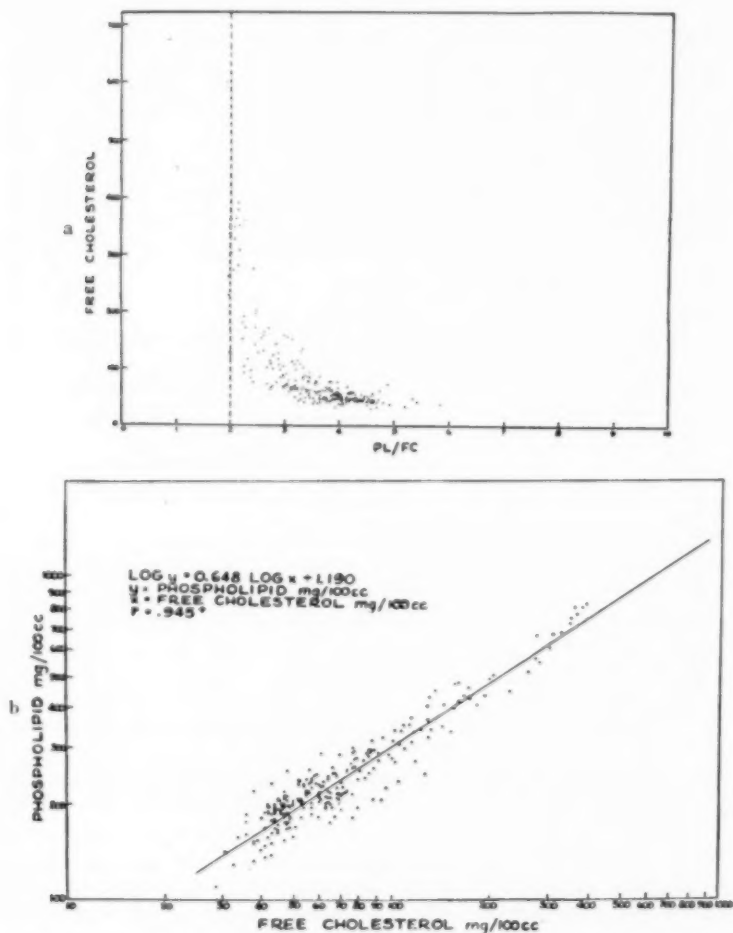


FIG. 2A (upper). The effect of the free cholesterol level on the ratio phospholipid/free cholesterol. B. (lower) The data from figure 1B are plotted on logarithmic axes.

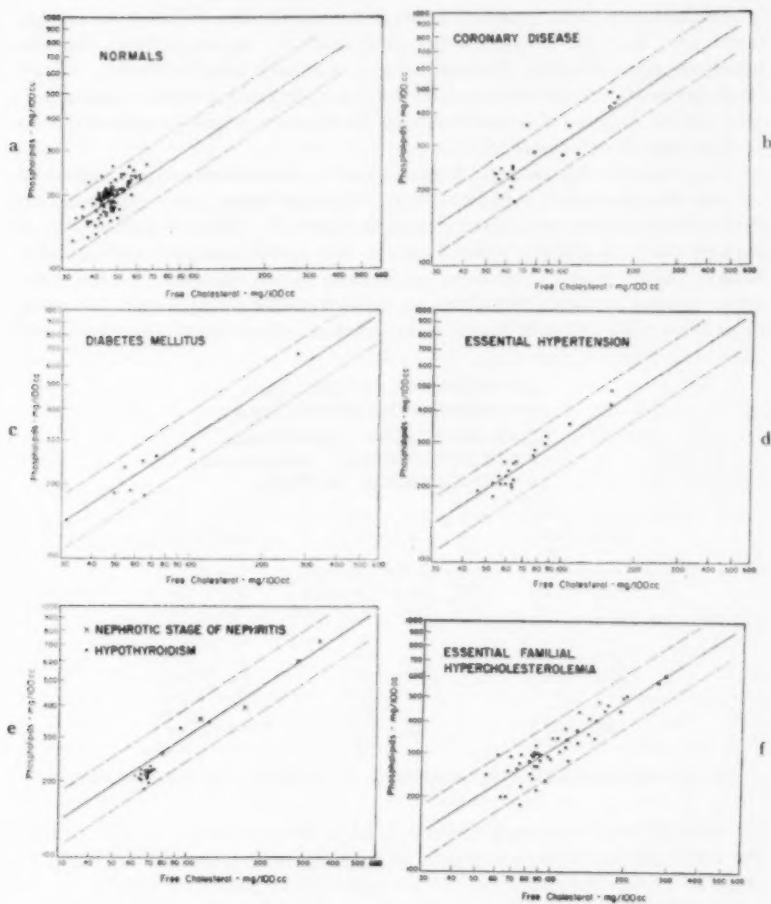


FIG. 3. The relationship between phospholipid and free cholesterol in apparently normal subjects and in several disease states related to the problem of atherosclerosis.

deviations of the logarithm of  $Y$ —the phospholipid value. No more than 5 per cent of the values should fall outside these lines, if the data are normally distributed. Out of the 102 determinations in this group, only three are more than two standard deviations away from the mean of the entire series.

3. *How is this relationship altered in diseases which are the manifestation of atherosclerotic vascular changes?*

In the upper right graph of figure 3 are plotted the values from our patients who had proved myocardial infarctions or angina pectoris, diseases which are predominantly the end result of coronary atherosclerosis. Of the 20 determinations, one falls outside our two standard deviation limits.

4. *How is this relationship altered in diseases which predispose to the development of atherosclerosis?*

As far as the diseases which predispose to atherosclerosis are concerned, our results in diabetes, hypertension, hypothyroidism and nephrosis are demonstrated in the next three graphs of figure 3. These diabetics were in various states of diabetic control: some had severe vascular complications, others little or none. Yet their distribution around the mean for the entire series seems to indicate that they too conform to the over-all rule. A group of patients with essential hypertension likewise shows good agreement with

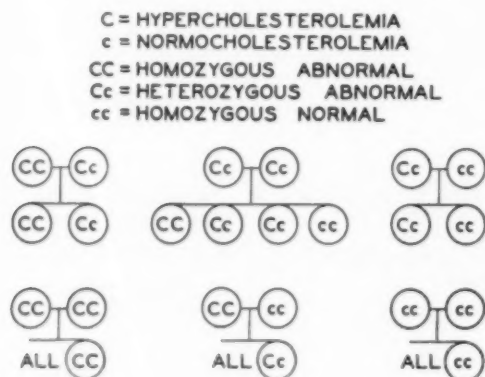


FIG. 4. Genetic patterns of various matings in essential familial hypercholesterolemia.

the straight line expressing the relationship for the entire group. And on the lower left are seen our results in hypothyroidism and in the nephrotic stage of glomerular nephritis. Once again, these patients conform.

5. *Are there diseases which show this same abnormality but are not associated with an abnormal degree of atherosclerosis?*

In 1948, Wilkinson, Hand and Fliegelman reported studies on a large kinship exhibiting the genetic abnormality that they termed "essential familial hypercholesterolemia."<sup>33</sup> They found that the abnormality was transmitted as an incomplete dominant (figure 4), with hypercholesterolemia alone where only one gene was inherited, but more severe hypercholesterolemia and xanthoma of the skin and tendons where the individual had inherited an abnormal gene from both parents. In their studies, they were unable to demonstrate a tendency to premature atherosclerosis in the heterozygous

abnormal group, but such a tendency was marked in the homozygous abnormal.

In figure 3 (lower right), we see plotted the values from some of these individuals, those at the upper end of the curve being the homozygous abnormal, whereas those at the lower end had inherited only the single gene. Again, the agreement with the over-all miscellaneous series is obvious.

Those who advocate the phospholipid-total cholesterol ratio have emphasized the observation that in myocardial infarction, xanthomatosis and such diseases, the average phospholipid-total cholesterol ratio is less than 1, whereas in the normal group it is usually greater. If one assumes that free cholesterol constitutes 30 per cent of the total cholesterol in these diseases, and that our equation for the relationship between phospholipid and free cholesterol is correct, it can be calculated that the free cholesterol value will be about 80 mg. per cent where the phospholipid-total cholesterol ratio is 1.00.

Applying the rule of inverse relationship between the ratio and the cholesterol value demonstrated in figure 2A, those individuals with free cholesterol greater than 80 mg./100 c.c. would have phospholipid-total cholesterol ratios less than 1. But the group in the range just above 80 mg. per cent were predominantly heterozygous and had no evidence of unusual degrees of atherosclerosis.

*6. Is there any other explanation for these alterations which have been observed?*

Each of the abnormal groups which we have discussed exhibits an average hypercholesteremia, which may be consistent in the given disease, or present only in certain individuals. This happens to be true even in our series of patients with essential hypertension. Since none of these diseases is characterized by marked liver dysfunction, we can assume that the free cholesterol constituted about 30 per cent of the total. Therefore, the phospholipid-total cholesterol ratio would bear a constant relationship to the phospholipid-free cholesterol ratio. For this reason, we can use figure 2A to test the effect of hypercholesteremia per se on the phospholipid-total cholesterol ratio. As noted before, the higher the cholesterol, the lower the ratio. Therefore, a group of individuals whose average cholesterol exceeds the normal average would inevitably have a lower average phospholipid-total cholesterol ratio. The average hypercholesteremia in such diseases as coronary sclerosis, hypothyroidism, nephrosis and diabetes can in itself explain the lower average phospholipid-total cholesterol ratios which have been reported.

#### SUMMARY

Going back to the questions we originally posed, we can say that the phospholipid-total cholesterol ratio is inherently unsound, since one of its components—total cholesterol—exists only in the imagination of the chemist. Under conditions where the free cholesterol forms a constant proportion

of the total cholesterol, a mathematical relationship can be demonstrated between phospholipid and total cholesterol, but this is a mathematical device and not a biological relationship. Diseases which are the end result of atherosclerosis or which predispose to this vascular lesion can be shown to have lower average phospholipid-free cholesterol and phospholipid-total cholesterol ratios than normal individuals, but they do not differ significantly in this respect from values predicted from a large miscellaneous group. Similar reductions in this ratio can be observed in individuals with essential familial hypercholesteremia who are genetically heterozygous abnormal, and who could not be shown to be especially prone to atherosclerosis. Finally, the decreased phospholipid-total cholesterol ratios observed in certain disease states simply reflect a higher average circulating cholesterol level.

#### CONCLUSION

Since, if given the total cholesterol value, one can predict the phospholipid-total cholesterol ratio within narrow limits (where liver failure is not present), it follows that this ratio can be no more useful as an index of atherosclerosis than the discredited total cholesterol itself.

#### BIBLIOGRAPHY

1. Davis, D., Stern, B., and Lesnick, G.: The lipid and cholesterol content of blood of patients with angina pectoris and arteriosclerosis, *Ann. Int. Med.* **11**: 354, 1937.
2. Barker, N. W.: Occlusive arterial disease of the lower extremities associated with lipemia and xanthoma tuberosum, *Ann. Int. Med.* **12**: 1891, 1939.
3. Steiner, A., and Domanski, B.: Serum cholesterol and atherosclerosis in chronic glomerulonephritis, *Am. J. M. Sc.* **204**: 79, 1942.
4. Steiner, A., and Domanski, B.: Serum cholesterol level in coronary arteriosclerosis, *Arch. Int. Med.* **71**: 397, 1943.
5. Boas, E. P., and Adlersberg, D.: Familial hypercholesterolemia (xanthomatosis) and atherosclerosis, *J. Mt. Sinai Hosp.* **12**: 84, 1945.
6. Lerman, J., and White, P. D.: Metabolic changes in young people with coronary heart disease, *J. Clin. Investigation* **25**: 914, 1946.
7. Gubner, R., and Ungerleider, H. E.: Arteriosclerosis, a statement of the problem, *Am. J. Med.* **6**: 60, 1949.
8. Moreton, J. R.: Atherosclerosis and alimentary hyperlipemia, *Science* **106**: 190, 1947.
9. Morrison, L. M., Berlin, P., and Gonzales, W. F.: Fat tolerance tests in coronary thrombosis, *Am. Heart J.* **38**: 477, 1949.
10. Gofman, J. W., Lindgren, F., Elliott, H., Mantz, W., Hewitt, J., Strisower, B., Herring, V., and Lyon, T. P.: The role of lipids and lipoproteins in atherosclerosis, *Science* **111**: 166, 1950.
11. Pomeranze, J., and Kunkel, H. G.: Serum lipids and atherosclerosis in diabetes mellitus, *Circulation* **2**: 474, 1950.
12. Morrison, L. M., Wolfson, E., and Berlin, P.: The relationship of cholesterol esterase to atherosclerosis, *Circulation* **2**: 479, 1950.
13. Sobel, H., and Morrison, L. M.: The action of saponin upon serum from atherosclerotic and nonatherosclerotic individuals, *Circulation* **2**: 480, 1950.
14. Keys, A.: Cholesterol, giant molecules, and atherosclerosis, presented June 15, 1951 before the Section of Internal Medicine, 100th Annual Session of the American Medical Association, Atlantic City, N. J.

15. Barr, D. P., Russ, E. M., and Eder, H. A.: Protein-lipid relationships in human plasma. II. In atherosclerosis and related conditions, *Am. J. Med.* **11**: 480, 1951.
16. Kellner, A., Correll, J. W., and Ladd, A. T.: Modification of experimental atherosclerosis by means of intravenous detergents, *Am. Heart J.* **38**: 460, 1949.
17. Davidson, J. D., Abell, L. L., and Kendall, F. E.: Serum lipids in experimental canine arteriosclerosis, *Am. Heart J.* **38**: 462, 1949.
18. Ahrens, E. H., and Kunkel, H. G.: The stabilization of serum lipid emulsions by serum phospholipids, *J. Exper. Med.* **90**: 409, 1949.
19. Thannhauser, S. J.: *Lipidoses: diseases of the cellular lipid metabolism*, 1950, Oxford University Press, New York, pp. 144, 218.
20. Morrison, L. M., Gonzales, P., and Wolfson, E.: The phospholipid/cholesterol ratio as a test for atherosclerosis, *Circulation* **2**: 472, 1950.
21. Gertler, M. M., and Garn, S. M.: Lipid interrelationship in health and in coronary artery disease, *Science* **112**: 14, 1950.
22. Boyd, E. M.: Oxidative micro-estimation of blood lipids, *Am. J. Clin. Path. Tech. Supp.* **2**: 77, 1938.
23. Fiske, C. H., and Subbarow, Y.: Colorimetric determination of phosphorus, *J. Biol. Chem.* **66**: 375, 1925.
24. Thannhauser, S. J.: Serum lipids and their value in diagnosis, *New England J. Med.* **237**: 515, 546 (Table IV), 1947.
25. Thannhauser, S. J.: *Lipidoses: diseases of the cellular lipid metabolism*, 1940, Oxford University Press, New York, p. 107.
26. Wilkinson, C. F., Jr.: Essential familial hypercholesterolemia: cutaneous, metabolic and hereditary aspects, *Bull. New York Acad. Med.* **26**: 670, 1950.  
Jackson, R. S., Wilkinson, C. F., Jr., Hand, E. A., Waldron, A. M., and Vogel, W. C.: The relationship between the phospholipids and the cholesterol in human plasma, *Circulation* **2**: 473, 1950.
27. Albrink, M. J., Man, E. B., and Peters, J. P.: Serum lipids in infectious hepatitis and obstructive jaundice, *J. Clin. Investigation* **29**: 781, 1950.
28. Gildea, E. F., Man, E. B., and Peters, J. P.: Serum lipids and proteins in hypothyroidism, *J. Clin. Investigation* **18**: 739, 1939.
29. Peters, J. P., and Man, E. B.: The interrelations of serum lipids in normal persons, *J. Clin. Investigation* **22**: 707, 1943.
30. Peters, J. P., and Man, E. B.: The interrelations of serum lipids in patients with thyroid disease, *J. Clin. Investigation* **22**: 715, 1943.
31. Peters, J. P., and Man, E. B.: The interrelations of serum lipids in patients with diseases of the kidneys, *J. Clin. Investigation* **22**: 721, 1943.
32. Man, E. B., Kartin, B. L., Durlacher, S. H., and Peters, J. P.: The lipids of serum and liver in patients with hepatic diseases, *J. Clin. Investigation* **24**: 623, 1945.
33. Wilkinson, C. F., Jr., Hand, E. A., and Fliegelman, M. T.: Essential familial hypercholesterolemia, *Ann. Int. Med.* **29**: 671, 1948.

## DIET AND ATHEROSCLEROSIS \*

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THE influence of fat in the diet has been described as an important factor in the causation of atherosclerosis by Dock,<sup>1</sup> Hueper,<sup>2</sup> Moreton,<sup>3</sup> Gofman,<sup>4</sup> Morrison<sup>5a</sup> and other observers. A related theory has developed which holds that atherosclerosis is "a disorder of lipid and/or lipoprotein metabolism," rather than the inevitable result of old age and the hopeless rusting out of the arteries.<sup>5b</sup>

Morrison<sup>5</sup> has recently attempted to subject this theory further to controlled, statistical study through his detailed observation, over a period of three years, of 100 ambulatory patients with proved coronary atherosclerosis. Fifty patients with atherosclerosis were placed on a low fat, low cholesterol diet with a daily intake of 20 to 25 gm. fat plus 75 mg. cholesterol. A control group of 50 patients with atherosclerosis did not receive the restricted diet. As both series consisted of patients who had been discharged recently from the hospital with proved coronary thrombosis and myocardial infarction, a condition which is associated with coronary atherosclerosis in approximately 90 per cent of patients,<sup>6</sup> these cases were deemed to be representative of proved atherosclerotic conditions with atherosclerotic effects (table 1).

The author found a statistically significant trend towards reduction of the mortality rate from recurrent coronary thrombosis during the period under study for patients who were placed on the low fat-low cholesterol diet. The serum cholesterol levels in patients on the restricted diet fell from a pre-treatment mean level of 312 mg. to a mean level of 220 mg. after three years of dietary control (table 2). The total serum lipids fell from a mean of 840 mg. prior to the dietary restriction of fat and cholesterol to 571 mg. following the dietary therapy. The mean drop of neutral fat was from 236 mg. to 120 mg. under the same circumstances. Only a small group of patients showed no statistically significant drops in serum cholesterol levels. It was hoped that this study would stimulate similar studies with larger series of patients, such as was accomplished with Dicumarol in the treatment of acute coronary thrombosis.

The term "atherosclerosis" is employed throughout this paper rather than "arteriosclerosis" in order to set forth at the outset the clinical difference and significance of the two processes. The phrase "atherosclerotic lesion" is used in this report to describe a condition in which the intimal and

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TABLE I

Survival Rates in Patients with Coronary Thrombosis and Infarction after Three Years

25 Gm. Fat-Cholesterol Intake			Normal Pre-Thrombosis Diet		
No. Cases	Deaths	Mortality (%)	No. Cases	Deaths	Mortality (%)
50	7	14	50	15	30

medial coats of the affected artery are involved with lipid, fatty or atheromatous plaques. When such a condition exists, consequent narrowing of the arterial lumen causes impairment of the circulation in the affected area, with resultant damage in the myocardium or cerebral tissue, for example. By contrast, the arteriosclerotic artery is affected by calcinosis of its medial coat, with little or no narrowing of the arterial lumen; hence little or no impairment of the local circulation results in the affected area. It has been estimated that about 85 per cent of lesions in the coronary and cerebral arterial fields are due to atherosclerotic or lipid-containing lesions.<sup>2</sup>

A number of reports appeared prior to World War II hypothesizing a relationship between the decreased incidence of atherosclerosis in certain countries and the fact that large segments of the populations of these countries had been following a low fat diet over a long period. The validity of such reports has been questioned because of the lack of biostatistical analysis of the data presented. The author has attempted to authenticate his report by reviewing statistics published in the past year concerning belligerent countries, where a low fat diet was universally prevalent during the World War II years.

The most recent information is from Norway, published this year.<sup>10</sup> Strom and Jensen report that in the war years 1940-1945 the Norwegian Ministry of Health noted a sharp reduction in the incidence of deaths from coronary atherosclerosis (figure 1). Figure 2 demonstrates the virtually perfect correlation between the drop in the atherosclerotic mortality rate and the drop in fat consumption, i.e., in the consumption of butter, milk, cheese and eggs. Strom and Jensen found that the reduction in mortality from

TABLE II

Serum Lipids after Three Years of Low Cholesterol-Low Fat Diet in 50 Patients with Coronary Thrombosis and Infarction

3 Years of 23 gm. Daily Fat Intake	Total Serum Lipids*	Total Serum Cholesterol	Serum Neutral Fats	Serum Phospho- lipids	Phospholipid Cholesterol Ratio
Before dieting	840	312	236	292	0.9
After dieting	571	220	120	231	1.1

\* Mg. mean values for all patients.

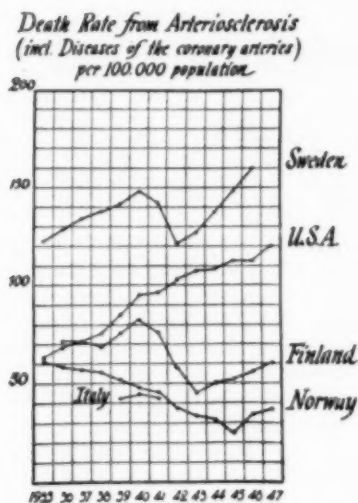


FIG. 1. Death rate from arteriosclerosis in Finland, Norway, Sweden and U. S. A., 1935 to 1947. (Malmros.)

coronary, cerebral and generalized arteriosclerosis was due solely to the sharp curtailment of fat and cholesterol in the diet. Reduction in weight did not appear to be directly related to the reduction in mortality rates.

These authors determined that mortality from what we describe as coronary arteriosclerosis was reduced by 31 per cent among the urban popula-

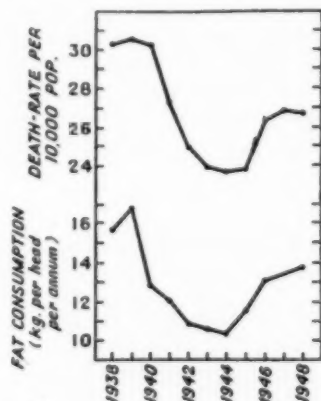


FIG. 2. Mortality from circulatory diseases corrected for age; consumption of fat in form of butter, milk, cheese and eggs. (Malmros.)

tion during each of the war years (table 3). A 22 per cent drop in the mortality rate occurred among the rural population. The Norwegian mortality rate was lowered even further because of the drop in deaths from cerebral arteriosclerosis and renal arteriosclerosis during the same period. During the war years there was, therefore, approximately a 50 per cent reduction in the mortality rate from arteriosclerosis in Norway, which reduction is solely attributable to the severe dietary restriction of fat and cholesterol and to the coincident reduction of calories, as pointed out by Strom and Jensen.

Turning now to England, we find that Himsworth has reported a recent study on the mortality rate from diabetes mellitus during the World War II years.<sup>11</sup> This study included data from both England and Wales. Figures from the Medical Research Council for England reveal that a 50 per cent reduction of mortality from diabetes was observed in patients over the age

TABLE III

Mortality from Apoplexy, Chronic Nephritis, and Arteriosclerosis Plus Chronic Myocarditis, in Urban and Rural Areas in 1938-1940 and 1943-1945

Areas	Apoplexy		Chronic Nephritis		Arteriosclerosis Plus Chronic Myocarditis	
	1938-40	1943-45	1938-40	1943-45	1938-40	1943-45
Urban:						
No. of deaths	2,771	2,467	693	351	2,876	2,042
Deaths per 10,000 pop. per year	11.1	9.6	2.8	1.4	11.5	7.8
Relative mortality	100.0	87.1	100.0	50.0	100.0	69.4
Rural:						
No. of deaths	6,171	5,437	1,402	768	6,225	5,039
Deaths per 10,000 pop. per year	9.8	8.3	2.2	1.2	9.9	7.7
Relative mortality	100.0	84.6	100.0	52.5	100.0	77.7

of 45 as a result of the marked curtailment of dietary fat, as rationed by the Ministry of Food Rationing. Himsworth's data indicate that over 100,000 diabetic patients in England alone have had their lives saved by the curtailment of fat in the diet since the government instituted the rationing of fat at the outset of the last war.

Examination of the graphs presented by Himsworth (figure 3) shows that the reduction of the mortality rate from diabetes occurred only in individuals over 45 years of age. Pickering<sup>12</sup> and the author have considered the possibility that the reduction in the mortality rate from diabetes which is attributable to the low fat intake was due rather to the decreased incidence of complicating vascular disease such as atherosclerosis. Unfortunately, no comparison of mortality rates between the war years and the post-war years is possible, as food rationing continues in England.

In France the mortality rates from atherosclerosis, as expressed in deaths due to coronary thrombosis and myocardial infarction, were reviewed for the author by Moine,\* of the French Ministry of Health. During World War II the fat intake in the diet was considerably curtailed in France, as well

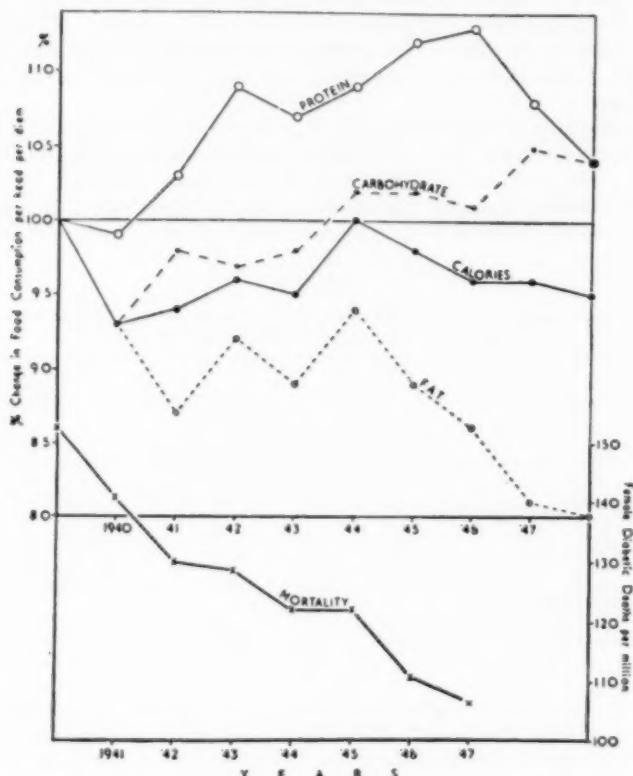


FIG. 3. England and Wales. Food consumption and female diabetic deaths. Showing the correlation between food consumption (2) and diabetic mortality rate. The female rate is chosen as less influenced by mobilization, and the curve is antedated one year to allow for time lag. (Himsworth.)

as in England and Wales and in the Scandinavian countries, and there occurred a similar statistically significant reduction in the mortality rate as compared with either the pre-war years or the post-war years, since the post-war years have seen a resumption of fat consumption at pre-war levels in

\* Appreciation is herewith expressed to M. Marcel Moine, Director, National Institute of Hygiene, France, for his courtesy in supplying these data.

France. For example, the average mortality rate from coronary thrombosis in France from 1941 to 1945, inclusive, was 20.6 per 100,000 population during the fat curtailment period. The mortality rate for 1945 to 1949, inclusive, after the resumption of normal fat consumption, was 25.5 per 100,000 population. This is in keeping with observations by such French clinicians as Besancon,<sup>13a</sup> LeComte,<sup>13b</sup> LeBlang<sup>13c</sup> and others, who noted during the later war years a sharp reduction in diseases of nutrition and metabolism such as diabetes mellitus and cirrhosis of the liver.

In Italy, Coppo and co-workers<sup>14a, b</sup> conducted studies in the incidence of coronary atherosclerosis (thrombosis) in the populations of two neighboring provincial areas. Studies performed recently on a series of patients who had eaten an unusually high fat diet, emphasizing pork products at each of the three daily meals, were compared with recent material concerning a series of patients whose daily fat intake was normal for the Italian population. A marked increase in the incidence of coronary and generalized atherosclerosis was found to have resulted from the high fat dietary intake.

Sweden's official mortality rates were reviewed by Malmros<sup>15</sup> and Henschen<sup>16</sup> in relation to the rationing of fats during the war years. These authors found that a 21 per cent drop in the mortality rates from coronary and generalized arteriosclerosis coincided with the establishment of the light to moderately severe fat rationing program during this period. As Sweden was not a belligerent in the last war, the curtailment of fat intake in that country was considerably less marked than the programs followed in the belligerent countries mentioned in this report, as pointed out by both Malmros<sup>15</sup> and Henschen.<sup>16</sup>

Finland and Denmark, with moderate rationing of fats during the war years, showed declines in mortality rate from coronary and generalized arteriosclerosis very similar to those of Sweden, as statistical reports published by Malmros<sup>15</sup> indicate.

A causal relationship between dietary fat intake and atherosclerosis has been similarly described during the past decade by investigators studying various national groups. A number of clinicians and pathologists have offered evidence in support of this theory, including Snapper,<sup>15</sup> in his investigations among the Chinese; Hueper,<sup>2</sup> among various, non-American national groups; Steiner, among the Okinawans; and Dock,<sup>1</sup> Gofman<sup>4</sup> and Morrison<sup>5</sup> in the United States, to mention but a few.

There is, however, an admitted difficulty in interpreting cause and effect relationships where the health of the entire population is involved. The possibility of mere coincidence must always be considered. One might jokingly claim, in disparagement of the statistical approach to the problem under discussion, that since the use of soap was sharply reduced during the war years in the countries discussed in this report, and that since the mortality rate from atherosclerosis was reduced at the same time, clearly soap (a fat) was a cause of atherosclerosis! Such an example serves to draw

attention to the fact that other factors in the pathogenesis of atherosclerosis are also demonstrable, and that danger lies in the attempt to oversimplify such a complex metabolic phenomenon as atherosclerosis.

Adlersberg et al.<sup>17</sup> and Wilkinson et al.<sup>18</sup> have recently shown the hereditary transmission of the susceptibility to hyperlipemia and coronary atherosclerosis, and these investigators are responsible for the concept of heredo-familial factors contributory to atherosclerosis, wherein genetic laws of transmission are operative in about one-third of the cases.

In a similar way, the influence and rôle of the endocrine system in the pathogenesis of atherosclerosis are also known,<sup>2</sup> as is the rôle of the liver in the regulation of lipid and lipoprotein metabolism<sup>7, 20</sup>; and the same is true of the subtle biochemical relationships of lipid and lipoprotein fractions such as cholesterol/phospholipid ratios,<sup>19, 20</sup> serum albumin and globulin fraction relationship,<sup>20, 21</sup> lipid enzymes, and other factors now under study. These considerations should serve to alert the investigator as well as the clinician to the dangers inherent in a one-sided view of the complex problem of atherosclerosis.

Perhaps one of the main reasons for the lack of complete acceptance of the theory that a disorder in lipid and lipoprotein metabolism is an important factor in the pathogenesis of atherosclerosis<sup>1-5</sup> has been the lack of universally acceptable statistical evidence substantiating the theory. Although most investigators readily admit the difficulties associated with unreserved acceptance of some evidence currently proffered in support of the above belief, nevertheless a heretofore hopeless attitude toward atherosclerosis is fast changing because of the rapid accumulation of undeniable facts presented in support of the lipoprotein concept in the etiology of coronary atherosclerosis.

From the practical point of view, a combined program of therapy in the management of coronary atherosclerosis would therefore appear justifiable at the present time. The best therapeutic results in the treatment of an individual case of atherosclerosis may be obtained with the following procedure. A careful history is taken which includes the state of health (or cause of death) of the parents, grandparents and siblings of both the patient and his parents. Biochemical analysis is made of the patient's blood serum for the determination of abnormalities in cholesterol-phospholipid ratios, serum lipid levels and, if possible, protein-bound iodine or basal metabolism levels. Obviously, these are supplemental to the customary clinical and laboratory evaluation of the patient.

In this way heredo-familial patterns may be traced effectively, and blood serum abnormalities which predispose to or are causal in the disease may be detected. Effective therapeutic measures are thus available centering about a low cholesterol-low fat diet for the reduction of serum cholesterol levels,<sup>22</sup> the use of lipotropic agents to increase the serum phospholipid levels,<sup>9</sup> and the employment of endocrine preparations, if any one or a combination of therapeutic agents are found to be indicated in a given case.<sup>23</sup>

Evidence has now been accumulated by various investigators to show that the above therapeutic approaches are effective in reducing the mortality rate and in instituting clinical improvement in patients with coronary atherosclerosis. More extensive studies and further investigations are therefore warranted by both investigators and clinicians in atherosclerosis, a disease which now ranks first as the cause of death in the United States.

#### SUMMARY AND CONCLUSIONS

1. The influence of a low fat-low cholesterol diet on reducing the mortality rate from coronary artery disease is reviewed from various countries during World War II years.
2. Fat and cholesterol intake in the diet appears to be statistically related to the incidence of death from coronary atherosclerosis.
3. The practical and clinical implications of the various dietary, biochemical and endocrine factors involved in atherosclerosis are discussed.

#### ACKNOWLEDGMENT

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#### BIBLIOGRAPHY

1. Dock, W.: The predilection of atherosclerosis for the coronary arteries, *J. A. M. A.* **121**: 875, 1946.
2. Hueper, W. C.: Arteriosclerosis. A review, *Arch. Path.* **38**: 162-364, 1944; **39**: 51-216, 1945.
3. Moreton, J. R.: Atherosclerosis and alimentary hyperlipemia, *Science* **106**: 190, 1947.
4. Gofman, W. J., Lindgren, F., Elliot, H., Mantz, W., Hewitt, J., Strisower, B., and Herring, V.: Role of lipids and lipoproteins in atherosclerosis, *Science* **111**: 166, 1950.
5. (a) Morrison, L. M.: Recent advances in the dietary and medicinal treatment of arteriosclerosis, *J. A. M. A.* **145**: 1232, 1951.  
(b) Morrison, L. M.: The role of the liver in atherosclerosis, *Ann. West. Med. and Surg.* **4**: 665, 1950.
6. Thannhauser, S. J.: *Lipoidoses: diseases of the cellular lipid metabolism*, 1940, Oxford University Press, New York.
7. Peters, J. P., and Van Slyke, D. D.: *Quantitative clinical chemistry*, Vol. 1, 1946, Williams & Wilkins Company, Baltimore.
8. Morrison, L. M.: Reduction of mortality rate in coronary thrombosis by a low fat-low cholesterol diet, *Am. Heart J.* **42**: 538, 1951.
9. Morrison, L. M., and Gonzalez, W. F.: Results of treatment of coronary atherosclerosis with choline, *Am. Heart J.* **39**: 729, 1950.
10. Strom, A., and Jensen, R. A.: Mortality from circulatory diseases in Norway, 1940-1945, *Lancet* **1**: 126, 1951.
11. Himsworth, H. P.: Diet in the etiology of human diabetes, *Proc. Roy. Soc. Med.* **42**: 323-326, 1949.
12. Pickering, G. W.: *Ibid.* **11**, Discussion.
13. (a) Besancon, J.: Personal communication.  
(b) LeComte, A.: Personal communication.  
(c) LeBlang, L.: Personal communication.

14. (a) Coppo, M., Bertoli, R., Prati, G., Gualanti, G., Lusiani, G. B., Pederzini, A., and Lorenzini, R.: Pathogenesis of arteriosclerosis, *Sett. med.* **20**: 499 (Oct.) 1950.  
(b) Coppo, M.: Visceral xanthomatosis, *Arch. stud. fisiopat. ricambio* **13**: 189 (Aug.) 1949.
15. Malmros, H.: The relation of nutrition to health, *Acta med. Scandinav. Supplement* **246**: 137-153, 1950.
16. (a) Henschen, F.: Die Arteriosklerose, *Verdankis Smaskrifter Nr.* **491**, 1947.  
(b) Henschen, F.: Pathogenesis of arteriosclerosis in the light of food restriction in Scandinavia during the war, *J. Gerontol.* **6**: 102, 1951.
17. Adlersberg, D., Parets, A. D., and Boas, E. D.: Familial hypercholesterolemia and atherosclerosis, *J. A. M. A.* **141**: 246, 1949.
18. Wilkinson, C. F., Blecha, E., and Reimer, A.: Is there a relation between diet and blood cholesterol? *Arch. Int. Med.* **85**: 389, 1950.
19. Kellner, A., Correll, J. W., and Ladd, A. T.: Modification of experimental atherosclerosis by means of intravenous detergents, *Am. Heart J.* **8**: 455, 1949.
20. Ahrens, E. H., and Kunkel, H. G.: Stabilization of serum lipid emulsions by serum phospholipids, *J. Exper. Med.* **90**: 409, 1949.
21. Leinwand, I., and Moore, D.: Simultaneous studies on the serum lipids and the electrophoretic pattern of the serum protein in man, *Am. Heart J.* **38**: 467, 1949.
22. Pomeranze, J.: Effect of diet and therapeutic agents on serum lipid tolerance in relationship to atherosclerosis, *J. Gerontol.* **6**: 134, 1951.
23. Morrison, L. M.: Serum cholesterol esterases in coronary atherosclerosis, *Circulation* **2**: 480, 1950.

## BASIC PRINCIPLES IN THE THERAPY OF DIABETES \*

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THE objectives in the treatment of diabetes are four:

1. To relieve symptoms.
2. To achieve and maintain normal nutrition.
3. To preserve whatever is left of the insulin producing power of the pancreas.
4. To prevent, postpone or minimize complications.

There is nothing easier in the practice of medicine than to relieve symptoms in the ordinary uncomplicated case of diabetes. A little diet and a little insulin will do wonders. This is at once a blessing and a curse—a curse because, with the mitigation of thirst and polyuria, many patients (and, I fear, too many doctors) see no reason to go further.

What are the reasons for going further? They have to do with the three other objectives of treatment which we have listed. With respect to nutrition, our chief enemy is obesity, the penalties of which are real and well recognized. In its dietary management, as well as in the management of other situations involving unusual caloric requirements, I should like to plead for realism and individualization. It is not true that a 1,200 calorie diet is a good diet for every patient who needs to lose weight. The obese housewife who has a large family and does all her own work will shrink satisfactorily on 2,000 calories if we can persuade her to stay with it, and our chances of doing so are better than if we nearly starve her with half that amount. Likewise, the manual laborer whose weight is normal must have upwards of 3,000 calories per day with liberal amounts of carbohydrate and protein, whether he is diabetic or not. Children at certain stages need almost as much. The prescription of grossly inadequate calories is an invitation to the patient to cheat—an invitation which he promptly accepts.

If a diet adequate for normal nutrition does not keep the urine essentially sugar free, the patient should receive insulin.

We have stated as our third objective the preservation of whatever is left of the insulin producing capacity of the pancreas. The implication is that this capacity is reduced in diabetes. The acknowledged importance of the pituitary-adrenal axis in the diabetic syndrome does not invalidate the older concept that the immediate cause of the disease is an absolute or relative deficiency of insulin. It is significant that permanent diabetes has never been produced experimentally except by methods which damage

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the pancreas. In the diabetes of man the rôle of the insulino-genic apparatus has received fresh emphasis from two directions. First, modern granule-specific stains have enabled pathologists to detect abnormalities of the beta cells in 80 per cent of patients dying with diabetes<sup>1</sup>—a far higher figure than was given 10 or 15 years ago. Second, the insulin content of the pancreas, as determined by bio-assay, has been found to be much reduced in diabetics as compared with nondiabetics. The earlier work on this subject by Scott and Fisher<sup>2</sup> has been confirmed in a report published this year by Wrenshall and his collaborators.<sup>3</sup> In a group of 57 hospitalized diabetic patients the extractable insulin of the pancreas averaged 1.02 units per gram, while in a comparable group of 52 nondiabetics the average was 2.37 units per gram. In terms of insulin per whole pancreas, the average figures were 77 units for the diabetics and 203 units for the nondiabetics.

One of the most interesting of Wrenshall's findings was that, in patients who had acquired diabetes in childhood or adolescence, the pancreas contained less than 10 per cent of the amount of insulin found in the pancreas of the adult diabetic; in some such cases there was almost no measurable insulin present.

The authors are careful to state that a low insulin content of the pancreas does not necessarily mean low insulin production. It is possible, with a given concentration in the beta cells, to have either a high rate of production and a rapid release into the blood, or a low rate of production and a slow release of the hormone. Bornstein and Lawrence,<sup>4</sup> however, have recently reported the absence of any detectable insulin in the blood of younger, severely diabetic patients with ketosis, whereas measurable though small amounts were present in the blood of older, obese diabetics without ketosis. It is unfortunate that determinations of plasma insulin and pancreatic insulin have not been made on the same patients. Nevertheless, the two observations taken together do suggest that diabetics as a class, and especially the younger diabetics, suffer from a deficiency of endogenous insulin.

If it be a reasonable probability that the pancreas is defective in most human diabetes, then we will want to protect it against further deterioration. If it is the young person with fully developed diabetes who has lost most of his ability to make insulin, then we will want to prevent the young diabetic, or any diabetic, from reaching that stage when he comes to us early. For to be without the power to make insulin is to be without the prime regulator of the blood sugar, without the means of smoothing out those distressing fluctuations due to variations in food intake, exercise and the absorption of injected insulin which characterize the labile diabetic. Doubtless there are many factors which are involved in this kind of instability, but failure of an insulin source which is responsive to rapidly changing needs, with resulting full dependence on exogenous insulin, seems likely to be one of them.

How, then, is the pancreas to be protected? The experimentalists have accumulated impressive evidence to the effect that if a certain degree of

damage has been inflicted on the beta cells of animals by any of a variety of methods, diabetes may result from, or be aggravated by, measures which promote hyperglycemia and thus increase the load placed upon those cells<sup>5, 6</sup>; indeed, normal animals have been made diabetic simply by prolonged injection of glucose.<sup>7</sup> Conversely, diabetes may be prevented, ameliorated or cured by measures which minimize hyperglycemia and lighten the load.<sup>5, 6, 8, 9, 10</sup> These experiments find their human counterpart in the work of Brush,<sup>11</sup> who reported some years ago that in children with diabetes of recent onset, vigorous, prolonged treatment with insulin to the point of hypoglycemia resulted in an insulin requirement of about one third that prevailing in children treated by less radical methods. The requirements of these patients eventually increased, but the observations indicate that the avoidance of high blood sugar at a time when complete loss of islet function has not yet taken place has a favorable influence upon the insulin producing power of the pancreas. The experience of Jackson<sup>12</sup> with diabetic children is consistent with this concept. Efforts to preserve that power should be made in all diabetic patients, particularly young patients in whom the onset of the disease is recent, by trying to keep the blood sugar as nearly normal as possible.

Our fourth objective is to prevent, minimize or postpone complications. In the current controversy as to whether this can be accomplished by good control of the underlying disease, it is sometimes forgotten that there are certain complications which are unquestionably the result of poor control. And let us define poor control, though this is dangerous, as meaning blood sugars habitually between 200 and 300 mg. per cent two to three hours after meals and the loss of more than 20 to 30 gm. of glucose each day in the urine, even though ketosis, polyuria and weight loss may be absent.

A common complication which occurs in patients of this kind is infection of the genitourinary tract, particularly in women. Vulvovaginitis is not serious and is amenable to treatment, but cystitis, pyelitis and pyelonephritis, whose advent is invited by a sugar-laden urine, are serious and may be fatal. These are often mixed infections which, once established, are resistant to all forms of treatment. Added to the Kimmelstiel-Wilson lesion, they play a vicious rôle in the high mortality from renal disease which accompanies diabetes of long standing.<sup>13</sup> They are, by and large, preventable by the avoidance of glycosuria. The rapid development of cataract in some young people with severe diabetes is well known. Whether susceptibility to cataract in older diabetics is related to the level of the blood sugar is uncertain, for adequate data are not available. It is abundantly clear, however, that in the experimental diabetes of the dog, the rat and the rabbit, cataract appears very commonly and that its incidence and severity are closely related to the degree of hyperglycemia and glycosuria.<sup>14, 15, 16, 17, 18, 19, 20, 21, 22</sup>

True diabetic neuritis, while sometimes seen in patients with mild diabetes, occurs much more frequently and severely in the presence of poor levels of control, and in my experience recovery does not take place without

careful regulation of diet and insulin. While a high blood sugar does not in itself cause diabetic coma, coma rarely occurs without it. It is the first signpost on the road to acidosis. It is like the sign on the rear of the motor truck: "If you can read this you are too damn close."

The most serious problem in diabetes today is vascular disease. Its cause is not known. The fact that retinopathy and premature arteriosclerosis are sometimes seen in patients with obviously mild diabetes has cast doubt on the theory that they are the consequence of hyperglycemia and hyperlipemia, and has raised the possibility that predisposition to vascular degeneration may be a constitutional or hereditary trait which merely accompanies, and is not the result of, diabetes itself. This possibility can be neither proved nor disproved at present. That diabetes per se, however, without the intervention of these unknown factors, *can* lead to premature vascular sclerosis is established in both man and animals. Lawrence,<sup>23</sup> for example, refers to such lesions in patients with long standing diabetes due to hemochromatosis and chronic relapsing pancreatitis. Furthermore, atherosclerosis of the aorta<sup>24</sup> and of the coronary arteries<sup>25</sup> has been observed in the experimental diabetes of dogs, and intercapillary glomerulosclerosis has been reported in pituitary diabetic dogs<sup>26, 27</sup> and in partially pancreatectomized rats.<sup>28</sup>

Regardless of constitutional factors, the solid clinical fact remains that the most advanced and extensive lesions are seen in patients with severe diabetes of long duration. The question is whether they can be prevented or delayed by the stringent control of glycosuria. This question does not necessarily imply that glucose as such is responsible, but is meant also to suggest that other factors associated with poor control, of which glycosuria is one manifestation, may be pathogenetic in this regard.

The final answer is not yet at hand. It is probably significant that the vascular lesions which have been found in experimental diabetes have developed for the most part in a milieu of unregulated hyperglycemia and glycosuria. Comparable observations with these factors minimized have not been reported. With respect to man, valid evidence bearing on this subject is exceedingly difficult to obtain. It is necessary to have access to large numbers of patients with diabetes of 15 to 20 years' duration, with different degrees of control and with trustworthy records which prove that control is what it is stated to be. Patients' records are not entirely reliable, especially in cases where careless management has prevailed, and the records of office visits reflect only the situation of the hour at intervals of weeks, months or years. Very few physicians or clinics are in a position to meet these requirements for a truly significant study. Bearing in mind the limitations we have mentioned, however, we may profitably consider two recent investigations which have been carried out as carefully and thoroughly as circumstances permit. The first is that of Jackson and his colleagues,<sup>29</sup> who recently reported on the reexamination of 75 patients whose disease, beginning before the age of 14.5 years, was of at least 10 years' duration; in half

the cases the duration was more than 15 years and in 11 it was over 20 years. Control ratings were established for each patient on the basis of his home tests, the hospital records, questionnaires and interval histories. One gets the impression that the home records of these patients were better than most. Highly significant correlations (at the 1 to 2 per cent level) as computed by the chi-square test were found between both the duration of the disease and the level of control on the one hand, and the incidence of both retinopathy and vascular calcification on the other.

The second study is that of Wilson, Root and Marble,<sup>13</sup> published in 1951. Of 247 carefully examined patients with onset of diabetes before age 20 and duration of from 10 to 34 years, 62 showed definite evidence of renal disease, and of these, 80 per cent were classified as poorly controlled; none of the seven patients with good or excellent control had nephritis. From a separate report by the Boston group,<sup>30</sup> we have abstracted the ophthalmoscopic findings in 103 patients with diabetes of at least 20 years' duration:

Retinopathy in 103 Cases of Diabetes of Long Duration

Control	None	Minimal	Moderate	Marked
Excellent	3	1	0	0
Good	10	5	4	0
Fair	9	4	6	3
Poor	12	6	28	12

The four patients with excellent control had no or minimal retinopathy. Of the 58 patients with poor control, 12 had no retinopathy, six had minimal, 28 moderate and 12 marked retinal disease. These data present a realistic and straightforward picture of the relation between the control of diabetes and the incidence of vascular disease. They tell us that, while a few patients with poorly controlled diabetes of long duration seem to have escaped, the majority have suffered more or less severe and irreparable damage. They tell us also that, while good control does not guarantee immunity to such lesions, it helps. It is comforting to have one's strong but unscientific clinical impressions thus confirmed by cold figures.

We must not forget the 12 patients who were free from retinal changes even though poorly controlled, or the few patients mentioned earlier who show vascular changes even with early and mild diabetes. These patients tell us that control is not the whole story, and we should admit that freely. Not knowing, however, what the other factors are, we should be unwilling to add to them the elements of hyperglycemia and glycosuria which, though operating in ways still obscure to us, carry their own penalty in terms of degenerative disease.

#### SUMMARY

The relief of symptoms and the achievement and maintenance of normal nutrition are objectives which can be easily realized in coöperative patients by the appropriate use of diet and insulin. Above and beyond these goals,

available evidence indicates that the preservation of the insulin producing power of the pancreas and the mitigation of infectious, metabolic and degenerative complications are materially aided, if not fully accomplished, by the proper control of hyperglycemia and glycosuria.

## BIBLIOGRAPHY

1. Bell, E. T.: The pathological anatomy of diabetes mellitus, *Illinois M. J.* **92**: 215, 1947.
2. Scott, D. A., and Fisher, A. M.: The insulin and the zinc content of normal and diabetic pancreas, *J. Clin. Investigation* **17**: 725, 1938.
3. Wrenshall, G. A., Bogoch, A., and Ritchie, R. C.: Extractable insulin of pancreas: correlation with pathological and clinical findings in diabetic and nondiabetic cases, *Diabetes* **1**: 87, 1952.
4. Bornstein, J., and Lawrence, R.: Two types of diabetes, with and without available plasma insulin, *Brit. M. J.* **1**: 732, 1951.
5. Allen, F. M.: Studies concerning diabetes, *J. A. M. A.* **63**: 939, 1914.
6. Houssay, B. A., and Martinez, C.: Experimental diabetes and diet, *Science* **105**: 548, 1947.
7. Dohan, F. C., and Lukens, F. D. W.: Lesions of the pancreatic islets produced in cats by administration of glucose, *Science* **105**: 183, 1947.
8. Lukens, F. D. W., and Dohan, F. C.: Pituitary-diabetes in the cat; recovery following insulin or dietary treatment, *Endocrinology* **30**: 175, 1942.
9. Lukens, F. D. W., Dohan, F. C., and Wolcott, M. W.: Pituitary-diabetes in the cat: recovery following phlorhizin treatment, *Endocrinology* **32**: 475, 1943.
10. Haist, R. E., Campbell, J., and Best, C. H.: Prevention of diabetes, *New England J. Med.* **223**: 607, 1940.
11. Brush, J. M.: Initial stabilization of the diabetic child, *Am. J. Dis. Child.* **67**: 429, 1944.
- 12a. Jackson, R. L., Boyd, J. D., and Smith, T. E.: Stabilization of the diabetic child, *Am. J. Dis. Child.* **59**: 322, 1940.
- 12b. Jackson, R. L., and McIntosh, C. B.: Treatment of the diabetic child with particular reference to the use of globin insulin, *Am. J. Dis. Child.* **70**: 307, 1945.
13. Wilson, J. L., Root, H. F., and Marble, A.: Diabetic nephropathy, *New England J. Med.* **245**: 513, 1951.
14. Chaikoff, I. L., and Lachman, G. S.: Occurrence of cataract in experimental pancreatic diabetes, *Proc. Soc. Exper. Biol. and Med.* **31**: 237, 1933.
15. Dohan, F., Fish, G., and Lukens, F.: Induction and course of permanent diabetes produced by anterior pituitary extract, *Endocrinology* **28**: 341, 1941.
16. Foglia, V. G., and Cramer, F. K.: Experimental production of diabetic cataract in the rat, *Proc. Soc. Exper. Biol. and Med.* **55**: 218, 1944.
17. Bailey, C. C., Bailey, D. T., and Leech, R. S.: Alloxan diabetes with diabetic complications, *New England J. Med.* **230**: 533, 1944.
18. Charalampous, F. C., and Hegsted, D. M.: Effect of age and diet on development of cataracts in the diabetic rat, *Am. J. Physiol.* **161**: 540, 1950.
19. Patterson, J. W.: Course of diabetes and development of cataracts after injecting dehydroascorbic acid and related substances, *Am. J. Physiol.* **165**: 61, 1951.
20. Duffy, E. J.: Alloxan diabetes in the rabbit, *J. Path. and Bact.* **57**: 199, 1945.
21. Rodriguez, R. R., and Krehl, W. A.: The influence of diet and insulin on the incidence of cataracts in diabetic rats, *Yale J. Biol. and Med.* **24**: 103, 1951.
22. Ricketts, H. T.: Unpublished observations.
23. Lawrence, R. D.: Types of human diabetes, *Brit. M. J.* **1**: 373, 1951.
24. Dragstedt, L. R.: The role of the pancreas in arteriosclerosis, *Biol. Symposia* **11**: 118, 1945.

25. Ricketts, H. T.: Unpublished observations.
26. Lukens, F. D. W., and Dohan, F. C.: Experimental pituitary diabetes of five years' duration with glomerulosclerosis, *Arch. Path.* **41**: 19, 1946.
27. Conn, J. W.: Personal communication.
28. Foglia, V. G., Mancini, R. E., and Cardoza, A. F.: Glomerular lesions in the diabetic rat, *Arch. Path.* **50**: 75, 1950.
29. Jackson, R. L., Hardin, R. C., Walker, G. L., Hendricks, A. B., and Kelly, H. G.: Degenerative changes in young diabetics in relationship to level of control, *Proc. Am. Diabetes A.* **9**: 309, 1949.
30. Wilson, J. L., Root, H. F., and Marble, A.: Prevention of degenerative vascular lesions in young patients by control of diabetes, *Am. J. M. Sc.* **221**: 479, 1951.

## DIABETIC COMA—A THERAPEUTIC PROBLEM\*

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THERE is a wide disparity in the mortality rates from diabetic coma, varying from approximately 1 per cent to as much as 50 per cent in presumably reputable hospitals. Low mortality rates are widely publicized but high rates are not. It is a safe conjecture that high rates would not be uncommon in a country-wide survey. If this surmise is correct, it would appear that fatalities from diabetic coma occur for want of an early diagnosis and early treatment, for want of specially trained personnel, and possibly, but not so likely, for want of laboratory facilities or a combination of these influences.

Delay in arriving at a diagnosis of diabetic coma is the lethal offender which permits the condition to pass from a stage in which very simple measures are promptly and favorably effective, into the more grave and multiple states associated with tissue starvation and seriously disturbed electrolyte values with peripheral vascular collapse. An early diagnosis of diabetic coma permits the stopping of these processes in their incipency.

### EARLY DIAGNOSIS

An early diagnosis will be made in most cases, and lives will be saved, if the urine is tested for sugar at once, in the home, in every case in which diabetic coma might be even a remote possibility, and especially if the acutely ill patient is a known diabetic or has a family history of diabetes. If a grade 4 reaction for glycosuria occurs one checks for ketonuria, realizing that in instances in which renal failure is prominent, ketonuria may be insignificant in the rare case. With glycosuria and corroborative clinical evidence, the diagnosis of diabetic coma may be secured by finding a grade 4 reaction for acetone bodies on testing the blood plasma. I have encountered no disease, other than diabetic ketosis, which gives these findings. Mary B. Wishart was the first to employ the Rothera test for the detection of excessive amounts of ketones in the blood. Actually, tests applied to the urine for the detection of acetone are suitable for testing the plasma.

The progression from mild ketonuria to severe ketonemia is illustrated in figure 1. The patient with grade 4 reactions for glycosuria and for plasma acetone is relatively resistant to insulin. Hence, it is quite safe to begin therapy at once *in the home* by administering regular insulin—100 units—and by having the patient drink 8 ounces of salty broth. It is remarkable how frequently the latter corrects nausea and alleviates vomiting and, as a result, reduces the precipitous trend toward hazardous alterations

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in the electrolyte balance. Then the patient is removed to a hospital, where studies as illustrated in figure 2 are carried out.

Occasionally one sees a patient who has the habit of going into diabetic coma. One such patient had found that by taking bicarbonate of soda he was, for a time, subjectively improved. The  $\text{CO}_2$  combining power may be above 20 vol. per cent as a result, but the plasma ketones will yield grade 4 reactions if the patient is truly in diabetic coma.

It may not be possible to be certain whether the acidosis is the result of renal failure or diabetic coma without a knowledge of the degree of ketonemia. This was well illustrated in the fatal case reported by Harwood,<sup>1</sup> who states: "It is evident from the persistence of nitrogen retention and of depression of the  $\text{CO}_2$  combining content that renal failure played an important part in this patient's acidosis. The absence of ketonuria raises some doubt whether diabetes was at all responsible for her condition. A blood ketone determination would have settled this point." A recent case reported by Root<sup>2</sup> also illustrates the importance of knowing the degree of ketonemia.

PLASMA & URINARY ACETONE IN DIABETIC KETOSIS  
(Illustrative)

	ACETONE IN URINE	ACETONE IN PLASMA
NORMAL	0	0
	+	0
	++	0
	+++	0
	++++	0
DEVELOPMENT OF SEVERE KETOSIS	++++	+
	++++	++ (PRE COMA)
	++++	+++
	++++	++++ (COMA)

FIG. 1. Relationship between ketonuria and hyperketonemia in the patient who is going into diabetic coma is presented.

In general, very low  $\text{CO}_2$  combining power values of the blood are considered to offer an unfavorable prognosis. This is by no means always the case. I recall one young patient who had a  $\text{CO}_2$  combining power of 8 vol. per cent but only a grade 2 hyperketonemia when the plasma was diluted 1:1 with normal saline. I shall say more about the diluted feature shortly. Recovery was prompt and with relatively small amounts of insulin. On the other hand, as emphasized by Butler,<sup>3</sup> a patient in the severe shocklike state may, because of lack of response to the acidosis by hyperventilation, have a more severe acidosis, "with a lower serum pH but higher  $\text{CO}_2$  concentration than the patient whose serum pH level is being defended by the vigorous hyperpnea lowering alveolar  $\text{CO}_2$  and serum  $\text{H}_2\text{CO}_3$ ."

For these reasons, and the not unimportant possibilities of inaccuracies which may creep into the determination of the  $\text{CO}_2$  combining power between 4:30 p.m. and 9:00 a.m. daily, weekends and holidays—in our hospital and in yours—we have adopted for clinical purposes, *glycosuria and a 4 plus*

DIABETIC COMA—SYMPTOMS AND THERAPY RECORD Pennsylvania Hospital												
Date	Half Day of Treatment Time	Name										
Hours of Treatment	0	1	2	3	4	5	6	7	8	9	10	11
Blood Sugar	*				*				*			*
Acetone	*				*				*			*
CO <sub>2</sub>	*				*				*			*
Hematocrit	*				*				*			*
Specific Gravity	*				*				*			*
Urea Nitrogen	*				*				*			*
Urine Sugar	•	•	•	•	•	•	•	•	•	•	•	•
Acetone	*		*		*		*		*		*	*
Culture	*											
Analysis	*								*			
Electrocardiogram	*				*				*			*
Blood Pressure	*	*	*	*	*		*		*		*	*
Other												

FIG. 2. An outline showing the studies and the intervals between tests indicated in a case of diabetic coma is presented.

reaction for acetone in the plasma as the criteria for the diagnosis of diabetic coma. Also, in our experience the qualitative tests for hyperketonemia on undiluted plasma and on the various dilutions mentioned below give more reliable indications of the gravity of the ketosis and of the prospective need for insulin than does a knowledge of the CO<sub>2</sub> combining power or sugar content of the serum.

#### THERAPY

*Insulin:* Too little insulin is often given in the early stages of therapy. Some patients require many hundreds of units of insulin in the first 24 hours, while others recover with relatively small amounts. We have been guilty of giving routine amounts of insulin at the outset of therapy and increasing the dosage only after smaller quantities proved to be inadequate.

For several years, however, we at the Pennsylvania Hospital have used the degree of ketonemia as a guide in determining the amount of insulin to be administered in the treatment for diabetic coma. When a grade 4 reaction for plasma ketones is found, a sample of plasma is diluted 1:1 with normal saline; if this dilution still gives a grade 4 reaction for acetone, the ketonemia is of severe degree and large amounts of insulin will be tolerated at the outset of therapy. This diluted mixture is further diluted 1:1 with normal saline, and if a grade 4 reaction is still elicited the ketosis is of a profound degree. In such cases, for some reason which is not clear, the apparent effectiveness of insulin is profoundly impaired; hence, and especially when the clinical condition of the patient is grave, as much as 300 units of regular insulin are given as the initial dose. On the other hand, patients exhibiting a grade 4 reaction for acetone in the undiluted plasma

but only grade 3 or even grade 2 reaction on the first dilution have been, in our experience, much more sensitive to insulin. An initial dose of 100 units of regular insulin—40 units intravenously and 60 units subcutaneously—with 25 units at one hour intervals until the undiluted plasma gives less than a grade 4 reaction, suffices to correct the ketosis promptly, as illustrated in the case of J. C. (figure 3). In this instance, the ketosis was corrected with only 160 units in the first 24 hours.

We have adopted the plan of giving 100 units of regular insulin as the initial dose if a grade 4 reaction for plasma acetone is determined only in the undiluted plasma, 200 units if this reaction is also obtained in the first dilution of the plasma, 300 units if this reaction is observed in the second dilution, and 400 if it occurs in the third dilution.

In cases of profound ketonemia, as much as 100 units or even more are given at half-hour intervals after the initial large dose until less than a grade 4 reaction for acetone in the undiluted plasma is attained. A decrease in ketone content of the diluted plasma and finally of the undiluted plasma is detectable before any apparent reduction in ketonuria is observed. When this occurs, a rapid return of sensitivity to insulin ensues and, to avoid the

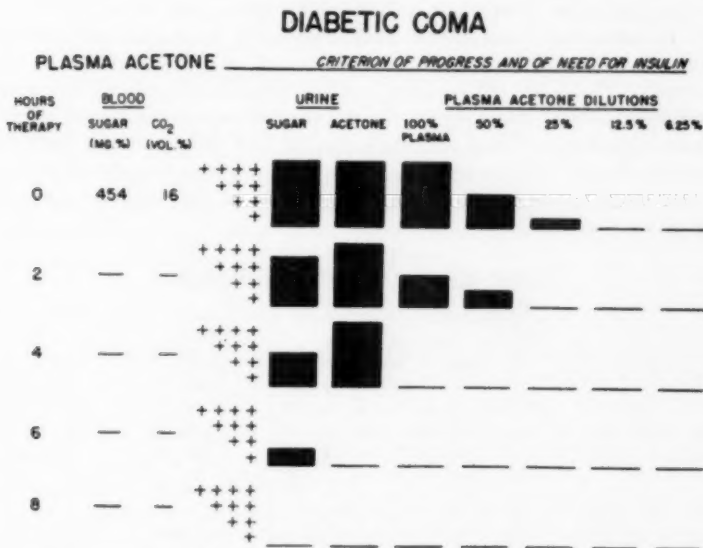


FIG. 3. The relatively mild degree of hyperketonemia, as indicated by only grade 2 reaction for plasma acetone on the first dilution (1:1) with normal saline, and the relatively small amount of insulin needed for its correction are illustrated.

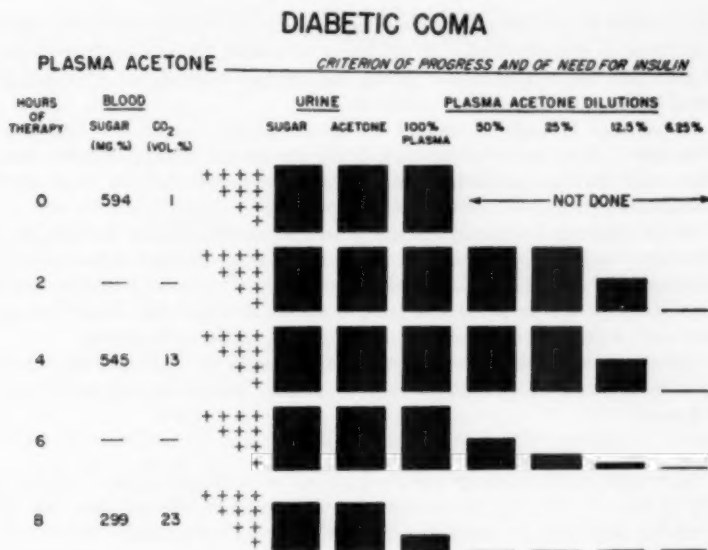
accumulative effect of large and frequently repeated doses of insulin, the amounts given are curtailed greatly and the administrations are reduced to one every four or six hours. The return of sensitivity to insulin and its relation to the degree of ketonemia are illustrated in figure 4. If the qualitative tests for ketonemia have become negative and glycosuria subsides, glucose is administered and insulin therapy is withheld until glycosuria returns.

The case of L. W. (figure 5) illustrates the larger amounts of insulin—905 units—in the first 24 hours of therapy, and their effects upon the ketonemia. In this instance, grade 4 reactions for acetone in the plasma persisted through the second dilution after two hours of treatment.

Tests for acetone in the plasma as guides to therapy give the clinician valuable and prompt bedside information. Though we do  $\text{CO}_2$  combining power determinations, they are not essential to satisfactory therapy and may even be misleading. In fact, we have treated successfully several patients in diabetic coma with only the laboratory information gained at the bedside. In these cases the degree of ketonemia as indicated by qualitative tests for plasma ketones was used as a guide as to the expected sensitivity of the insulin, and through the use of an indwelling catheter and testing the urine for sugar at hourly intervals it was a simple matter to maintain glycosuria until the ketosis was corrected. This is probably an oversimplification of therapy, and it would not apply in the unusual case in which anuria has developed. However, the simplicity of the criteria—diagnostic and guide to therapy outlined above—gives to the practitioner methods that permit such an early diagnosis and such early therapy that the grave state indicated by anuria should rarely be permitted to develop. These remarks should not be considered as deprecating the use of whatever scientific data can be

PLASMA ACETONE & SENSITIVITY TO INSULIN (DIABETIC COMA—CASE V. H. - APRIL 1952)									
HOURS OF THERAPY	TESTS PLASMA FOR ACETONE						$\text{CO}_2$ VOL %	INSULIN (UNITS)	
	UNDIL	50%	25%	12.5%	6.25%	3.12%			
0	++++	++++	++++	++	+	TR	12	250	
2	++++	++++	++	+	TR	TR		150	
4	++++	+++	+	TR	0	0	29	200	
6	+++	++	TR	TR	0	0		200	
8	+++	++	TR	TR	0	0	45	20	
10	++	+	TR	0	0	0	44	0	
12	+	TR	TR	0	0	0	45	0	
16	0	0	0	0	0	0		30	
18	0	0	0	0	0	0		0	

FIG. 4. Data from the case of V. H. indicate: a severe grade of ketosis; a high initial need for insulin, and a parallel relationship between the decreasing ketonemia and the returning sensitivity to insulin.



CASE OF L.W.: INSULIN DOSAGE, FIRST 24 HOURS - 905 UNITS

FIG. 5. A severe degree of hyperketonemia as indicated by the grade 4 reaction for plasma acetone on the second and grade 2 on the third dilution (1:1) with normal saline and the relatively greater need for insulin, are illustrated in this case of diabetic coma.

secured. Where such data are available and reliable, the mortality from diabetic coma is likely to be low. Where such data are not available or not reliable, a workable and simple substitute is available.

#### FLUIDS AND ELECTROLYTES

Characteristically, there are great deficits of fluid, sodium chloride and potassium, inorganic phosphorus and magnesium, although the body deficits of the latter three are not apparent until therapy has been started. A complete history will indicate the approximate duration of the unfavorable processes. It permits an appraisal of the duration of the adaptive changes which tend to obscure deficits.

To the adult in diabetic coma, fluids are given intravenously as rapidly as 8 to 10 c.c. per minute while the systolic blood pressure is below 100 mm. of Hg and while the hematocrit reading is above normal. Initially, 2 liters of normal saline are given intravenously. The amount of sodium chloride (17 gm.) thus provided is adequate to relieve the immediate needs, though by no means correcting the total deficit. A third and indeed a fourth liter of

normal saline are indicated if urine is being excreted rapidly and if the hematocrit value is still elevated. If evidences of severe tissue dehydration persist after the hematocrit value closely approaches normal, we give further normal saline by subcutaneous infusion.

No attempt is made to correct deficits completely in the first few hours of therapy. The aim is to reestablish the means for normal cellular metabolism with insulin, adequate fluids and electrolytes to care for basic needs and sufficient surplus to correct deficits gradually.

In the occasional instance where a profound shocklike state develops early in therapy, we have given plasma in one vein while normal saline was administered in another with satisfactory results. We have rarely given transfusions of whole blood but have done so if, after the initial therapy, there were evidences of hemoglobin or blood protein deficiencies.

Intravenous administrations are discontinued as soon as the patient can take adequate fluids orally. This is usually after from six to 10 hours of therapy.

#### POTASSIUM

Although electrocardiographic evidences of hypopotassemia develop as early as three hours after therapy has been started,<sup>4</sup> the clinical risk from the increasing depletion of potassium probably begins considerably later—after six to 12 hours of therapy. It has been my impression that hypopotassemia is detected very early by electrocardiography, and that clinical danger from the depletion of this electrolyte is postponed several hours at least. It has been difficult to convince interns and residents of the supersensitiveness of the electrocardiogram and of the hours of grace between the time when hypopotassemia is first indicated electrocardiographically and the approach of real clinical danger. When the influences of dilution, utilization and excretion factors are asserted, we give potassium chloride, orally, 1 gm. every four hours for five to eight doses, beginning after six hours of therapy, provided *renal function is good and urine is being excreted freely*. There is no apparent objection to giving potassium intravenously at a slow rate and in a 1.14 per cent solution until evidences of hypopotassemia are erased from the electrocardiogram. Indeed, this is desirable if its administration orally is impracticable. It would appear that, in view of the speed with which a clinical crisis from hypopotassemia can develop and end fatally, to avoid giving potassium after six hours of therapy when there are evidences of hypopotassemia is to run needless risk.

The foregoing measures will suffice in most cases of diabetic coma, but for patients with *profound ketonemia* there is need for more energetic correction of disturbances in the electrolyte balances. The plan recommended by Butler<sup>5</sup> has been reported upon favorably. This comprises, after the initial hydration and with the patient secreting urine and with the circulation satisfactory, the administration of 3 to 4 c.c. (50 drops) per minute of a multiple electrolyte solution of the following components:

Water c.c.	Sodium mEq.	Chloride mEq.	Potassium mEq.	Magnesium mEq.	Phosphorus mEq.	Glucose gm.
1000	42	35	30	5	16	75

As this solution is not given at the outset of therapy it is probable that the glucose content can do no harm, even theoretically. There is no need for glucose parenterally while extreme degrees of hyperglycemia persist. It is believed by Joslin and others that glucose given at this stage is harmful on the basis of increased cellular dehydration, increased resistance to insulin, and its diuretic effect. With restoration of the blood sugar to conservative levels—below 300 mg. per 100 c.c.—glucose given parenterally is indicated if oral feeding is impractical at this time. It will protect against the danger of a rapidly developing hypoglycemia in patients who become sensitive to insulin rapidly and at a time when their glycogen stores are depleted; it alleviates tissue starvation and is an important agent in reducing the excessive production of ketones. Ordinarily we begin parenteral glucose therapy after six or eight hours of therapy unless adequate oral intake at this time is practicable.

#### ALKALI

The disappearance of excessive keto-acids and the release of base that accompany therapy make the routine use of alkali unnecessary. However, if the degree of ketosis is extreme and the patient is markedly hyperpneic, we give sodium-R-lactate solution in an amount calculated to raise the  $\text{CO}_2$  combining power 10 to 15 vol. per cent *and no more*. Larger amounts are considered to carry unnecessary risk because they intensify the trend to an alkalosis which follows the correction of the ketosis.

#### FURTHER MEASURES

Every effort is made to detect, evaluate and correct the complication which precipitates the ketosis. Gastric lavage is done in patients having abdominal distention, persistence of vomiting or manifest tenderness on palpation of the abdomen.

#### SUMMARY AND CONCLUSION

The advantages of early diagnosis of diabetic coma have been stressed. Early diagnosis is possible by simply finding grade 4 positive qualitative tests for glycosuria and ketonemia in the subject with clinical evidences of ketosis. Initial therapy with insulin, fluids and sodium chloride is started at once—in the home. The importance of the degree of ketonemia as an indication of the gravity of coma and as an indicator for the amount of the initial doses of insulin has been stressed. Methods dealing with insulin

therapy, hydration and electrolyte, glucose and alkali therapy as employed at the Pennsylvania Hospital have been presented.

## BIBLIOGRAPHY

1. Harwood, R.: Diabetic acidosis, *New England J. Med.* **245**: 1, 1951.
2. Root, H. F., Story, R. D., and Cortesi, J. B.: Diabetic coma versus diabetic nephropathy, *New England J. Med.* **245**: 765, 1951.
3. Butler, A. M.: Diabetic coma, *New England J. Med.* **243**: 648, 1950.
4. Bellet, S., Nadler, C. S., Gazes, P. C., and Lanning, M.: Effect of vomiting due to intestinal obstruction on the serum potassium, *Am. J. Med.* **6**: 712, 1949.

## ACUTE RESPIRATORY FAILURE IN MULTIPLE SCLEROSIS AND ITS MANAGEMENT\*

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THE manifestations of acute multiple sclerosis are often fulminating and massively incapacitating but are also likely to subside completely.<sup>1</sup> In some instances the illness may lead rapidly to death, although the fatal episode may have been preceded by lesser attacks which have subsided.<sup>2</sup>

Several authors have described in considerable clinical detail acute, fatal attacks of multiple sclerosis.<sup>3</sup> The patients discussed have rapidly developed quadriplegia or bulbar dysfunctions or both prior to death. Occasionally they have been observed to be dyspneic or to evidence Cheyne-Stokes respiration. One author has made the undocumented statement that a patient with acute multiple sclerosis may die with "respiratory failure."<sup>4</sup> Otherwise we have been unable to find in the literature any reference to the rôle of ventilatory failure as a cause of death in acute multiple sclerosis. The possibility of maintaining a patient with artificial respiration during an acute exacerbation of multiple sclerosis until the patient recovers has not, to our knowledge, been reported.

Our recent experience with four patients with acute multiple sclerosis, all of whom showed ventilatory failure, has led us to the belief that unrecognized respiratory failure has been the cause of death in patients with acute multiple sclerosis. Because the acute episode of the disease usually subsides remarkably unless fatal, we present our cases to emphasize the life-saving rôle of artificial respiration in this clinical situation.

### CASE REPORTS

*Case 1.* In March, 1951, a 30 year old white man developed, within a period of 10 minutes, right-sided weakness, dysarthria and staggering gait. He improved rapidly within the next few days and was asymptomatic after six weeks.

In November he experienced a sensation of "coldness," followed by weakness of the left hand and forearm, associated with nausea and vomiting. This was followed in a few days by difficulty in walking, weakness and numbness of the entire left side of the body, difficulty initiating urination, and a transient episode of diplopia.

On admission to this hospital on November 30 there were a marked weakness of the left upper extremity and weakness of the left intercostal and abdominal muscles. The power of the lower extremities was also reduced, more markedly on the left. The deep tendon reflexes of all extremities were hyperactive. There were bilaterally positive Hoffmann's signs and ankle clonus, but no response to plantar stimulation. Vibration, position and stereognostic functions were diminished in the left upper

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extremity. Romberg's sign was positive. The gait was broad based, and there was a slapping motion of the left foot.

Shortly after admission he developed dysdiadochokinesia and coarse intention tremor of all extremities. Improvement occurred rapidly, so that by December 10 there remained only generalized hyperreflexia and impaired sensory function of the left hand.

On December 13 the patient awoke with marked vertigo, nausea and vomiting. On arising his blood pressure was 110/90 mm. of Hg; pulse, 160; temperature, 100° F., and white blood cells, 31,000. Vertigo, nausea and vomiting subsided that afternoon, and his blood pressure dropped to 88/70 mm. of Hg and the white blood cells to 26,000. There was a brief period of disorientation. The patient was weak and pale, perspired freely and had a marked tachycardia. Serial electrocardiograms indicated an antero-septal subendocardial infarct. In the evening of December 15 the patient became dyspneic, his breathing shallow and rapid. There was no visible descent of the diaphragms, and thoracic excursions were markedly reduced. At this time he was almost aphonic; he could make only weak ataxic movements of all extremities, had urinary retention and felt "numb all over." He was placed in a Drinker respirator and his temperature, pulse and blood pressure soon returned to normal. However, his downward course continued so that, after being in the respirator for two days, he became completely quadriplegic, and on the third day there was a complete sensory loss up to C-2. He also showed nystagmus on lateral gaze and complained of diplopia. Although he was dysphonic and unable to cough effectively, there was no difficulty in articulation, chewing, swallowing or protruding the tongue. On December 19, in this quadriplegic state, his vital capacity was 350 c.c. On December 20, with the beginning return of sensation and some feeble movements of three extremities, the vital capacity rose to 400 c.c. On December 21 he could move all extremities and the vital capacity was 750 c.c. By December 26 he was able to stay out of the respirator for three hours, and vital capacity had increased to 1,300 c.c. The use of the respirator was discontinued completely on January 1, 1952 (after 16 days), when his vital capacity was 1,700 c.c., and by January 7 his vital capacity was 2,500 c.c. By the time he was removed from the respirator his urinary function had returned to normal, but there were still a generalized weakness, ataxia, hyperreflexia of all limbs, impaired stereognosis in the left hand, bilaterally positive Hoffmann's signs and flexor plantar responses. By the time of his discharge, on January 25, he had only a residual hyperreflexia.

*Comment:* A 30 year old white male, during his third acute episode of multiple sclerosis, suddenly developed dyspnea and shallow, rapid breathing, with markedly decreased thoracic excursions and no movement of the diaphragms. His vital capacity was 350 c.c. of air. After transfer to a Drinker respirator he became completely quadriplegic. After 16 days in the respirator his motor and respiratory function improved. The patient was discharged asymptomatic 25 days later.

*Case 2.* A 25 year old white man was admitted on July 16, 1951, with a two month history of weakness of the legs, ataxic gait and impotence. The day prior to admission he complained of numbness of the right hand, followed by awkwardness in the use of both hands, and then numbness of the left hand. A fine horizontal nystagmus was found on right lateral gaze, with poor convergence and weakness of the right facial muscles. There were weakness, ataxia, hyperreflexia and positive Hoffmann's signs in both upper extremities, and all sensory modalities were diminished in both hands. Superficial abdominal reflexes were absent. The left lower extremity was weak and showed increased resistance to passive stretch and foot drop, and the deep

tendon reflexes were hyperactive. There was marked ataxia of both lower extremities, and Romberg's sign was positive.

The only abnormal laboratory findings were the presence of 25 lymphocytes and a Lange D curve <sup>2</sup> in the spinal fluid.

During the first three days after admission he gradually developed urinary retention, vertigo and weakness of the right arm and leg, then weakness of the left arm and leg and dysarthria.

On July 30 his rectal temperature was 100 to 101° F.; blood pressure, 120/80 mm. of Hg; pulse, 120; respirations, 32. He complained of being dyspneic, and it was found that there were marked decrease in the amplitude of chest movements and slight cyanosis of the nails. There was radiographic evidence of only slight movements of the diaphragms. Arterial oxygen saturation was 91 per cent. The patient was placed in a Drinker respirator, and his pulse then dropped to 90. On the second day in the respirator he had loss of all sensation up to second thoracic segment on the right and fourth thoracic on the left, and a spastic quadriparesis. At that time he could not remain out of the respirator for one hour without becoming dyspneic and cyanotic. There was no evidence of bulbar dysfunction.

While in the respirator his white blood cells were 12,000 to 19,000, the sedimentation rate was 49 mm. per hour, and there were white cells and albumin in the urine. The spinal fluid was normal but for 39 lymphocytes. On August 2 the patient became afebrile, and on August 6 he was able to leave the respirator with no clinical evidence of respiratory insufficiency. The power of his extremities also gradually improved, so that he was able to walk unaided by August 14. He still had nystagmus, increased resistance to passive stretch, hyperreflexia of all extremities and hypesthesia of both palms. At the time of discharge, on December 27, his condition was markedly improved despite mild residual weakness of the legs and ataxia.

*Comment:* A 25 year old white male with multiple sclerosis had a two month story of leg and bladder dysfunction. During an acute attack affecting his upper extremities he suddenly became dyspneic and cyanotic and had marked decrease in movements of the chest cage. His arterial oxygen saturation was 91 per cent. After transfer to a Drinker respirator he became quadriparetic. After seven days artificial respiration was no longer necessary. The patient improved steadily and was discharged four months later with only slight weakness and ataxia of the legs.

*Case 3.* A 48 year old white man was admitted for the first time on August 15, 1947, with a chief complaint of stiffness of the right leg of 10 years' duration. In 1943 he had noted precipitate micturition and paresthesias of both palms. Ataxic gait developed in 1945 and progressed to the time of admission. On admission the general physical examination was normal.

The neurologic examination showed hyperreflexia of all extremities, with positive Hoffmann's sign on the right, bilateral ankle clonus and extensor plantar responses. There was adiadochokinesia of all extremities, more marked on the right. The gait was spastic and ataxic. Two-point discrimination was impaired on the left fourth and fifth fingers, and vibration and position sense were absent in the toes.

Complete blood count, urinalysis, blood serologic reaction, spinal fluid examination and roentgenograms of the chest and skull were normal. Cystometrograms revealed a neurogenic bladder. A cervical myelogram was normal.

On June 1, 1948, it was observed that he had increased difficulty in walking, that there was a rotatory and horizontal nystagmus, and that all sensory modalities were markedly diminished below T-5.

On the evening of August 26 the patient complained of severe painless dyspnea, he was pale and sweaty and now had a right facial paresis. His blood pressure was 90/60 mm. of Hg. Electrocardiogram and roentgenograms of the chest were normal. He was placed in an oxygen tent but remained pale, cold and apprehensive, and his respirations were rapid, shallow and labored. The next morning his blood pressure was 145/105 mm. of Hg and his pulse was 128. There were also a right palatal weakness and absent gag and cough reflexes. The left upper and both lower extremities became flaccid and areflexic. At this time there were no thoracic excursions, and only weak abdominal breathing was observed. The patient was dysphonic and could not cough or expectorate effectively. By 2:00 p.m. on August 27, diaphragmatic action had become still weaker, and the patient lost consciousness. His pulse was 160. Endotracheal aspiration of thick mucus had to be performed because of accumulated secretions which could not be coughed up, but this did not prevent his death as he was being transferred to a respirator at 7:00 p.m. that same day.

Postmortem gross diagnoses were: (1) multiple sclerosis with numerous fresh lesions in the brain stem and spinal cord; (2) bilateral bronchopneumonia; (3) aortic and coronary sclerosis; (4) chronic cystitis.

Histologic examination by Dr. Abner Wolf demonstrated the following finding in the nervous system: There were many scattered areas of demyelination in both hemispheres, the brain stem and spinal cord. Fresh lesions were found in the tegmentum of the pons, and in the region of the fifth and seventh cranial nerve nuclei and spinal cord. The medulla was not involved. There were poorly outlined plaques in the posterior columns and lesions involving most of the lateral columns in the lower cervical segments. In the upper thoracic segments there were lesions involving almost the entire cross section of the cord. Further caudad sections through the lumbar segments revealed central, lateral, anterior and posterior demyelinating lesions. Some lesions showed perivascular accumulation of mononuclear cells and microglial proliferation in addition to the astrocytic proliferation and axonal loss.

*Comment:* A 48 year old white male with multiple sclerosis had a 10 year history of weakness of the legs, urinary dysfunction and ataxia. He suddenly developed painless dyspnea and was capable of only shallow, labored respiration. As a flaccid quadriplegia developed, all thoracic movements disappeared. The gag and cough reflexes were absent. Treatment with oxygen and suction was ineffective, and the patient died while being transferred to a respirator. Postmortem examination showed the changes of multiple sclerosis, with many fresh lesions in the upper brain stem and entire spinal cord.

*Case 4.* In April, 1951, a 37 year old white male suddenly developed "dizziness," nausea, blurring of vision and weakness of the right arm and leg, all of which disappeared in 30 seconds. The next day he complained of generalized weakness, necessitating bed-rest, which subsided after about five days. On July 4 he had another brief episode of "dizziness," nausea and vomiting. One week later there was an abrupt onset of diplopia, dysphagia and right hemiplegia, which persisted until his admission on July 19. The day before admission he noticed numbness of the left side of the body, and the left extremities became weak.

On admission his blood pressure was 180/120 mm. of Hg; temperature, 99.8° F.; pulse, 100; respirations, 24. His lungs were clear except for occasional rhonchi which disappeared after tracheal aspiration. His eyes were deviated to the right because of paralysis of left lateral gaze. There was nystagmus on superior and

inferior gaze and dissociated nystagmus on right lateral gaze. There were ptosis of the right lid and a right lower facial weakness. There was a flaccid quadriparesis, with complete paralysis on the left and marked paresis on the right. Sensation was preserved. There was no dysarthria. The uvula, tongue and jaw moved normally. He could talk only in a whisper. There was marked depression of thoracic excursions. Respirations were labored.

Repeated aspirations of the trachea and pharynx had to be performed to remove accumulated secretions which the patient could not cough up. Respirations averaged 24 per minute and dropped to four per minute one hour before death. He died 32 hours after admission.

*Comment:* A 37 year old white male, with recurrent symptoms of multiple sclerosis during the previous four months, suddenly developed a flaccid quadriparesis. There were dysphonia, markedly diminished thoracic excursions and labored respiration. Suction of the throat and pharynx was not helpful, and respirations decreased to four per minute before death, which occurred 32 hours after admission.

#### DISCUSSION

The four patients described have had a clinical course typical of multiple sclerosis. Each developed an episode of severe respiratory failure in the course of their illness. These patients had had previous neurologic deficits at the time the serious respiratory difficulty developed, but there are reports indicating that even the first episode of multiple sclerosis may be fatal.<sup>3</sup>

In all four patients a critical respiratory difficulty occurred. In two instances this was fatal, whereas in the other two a fatal outcome was averted by the early use of a Drinker respirator. Treatment with artificial respiration was chosen because the respiratory dysfunction was clearly attributable to ventilatory insufficiency. It was characterized by painless dyspnea, tachypnea and tachycardia. The expansion of the chest and excursions of the diaphragm were markedly reduced. There were an associated decreased vital capacity and a low arterial oxygen saturation. Cyanosis was observed in only one patient.

The patients with respiratory failure had certain distinctive features. Each developed a quadriparesis and depression of thoracic excursions as part of a rapid change in their neurologic status. All four were spastic at one time, but two later became flaccid. Three patients had a segmental level of sensory loss. It should be noted that dyspnea, tachycardia and respiratory depression were already present in each case even before there was the complete development of quadriparesis, and that paresis of the extremities increased in two cases after respirator therapy was instituted. Hence mild dyspnea, tachycardia and tachypnea in multiple sclerosis may portend the further development of quadriparesis and potentially fatal respiratory depression.

We were impressed by the absence of lower brain stem dysfunctions, which were seen only in case 3. This preservation of bulbar function greatly

simplified respirator management and made tracheotomy less urgent. All patients were febrile as they entered the acute episode of ventilatory insufficiency.

The lack of bulbar dysfunction, the quadriparesis and the high sensory levels indicated the presence of spinal cord lesions, involving pyramidal tracts bilaterally and possibly anterior horns in the cervical and thoracic spinal cord. This clinical estimation was proved sound by the autopsy findings in case 3, in which there were extensive fresh lesions throughout the entire spinal cord but no lesions of the medulla.

In the treatment of acute ventilatory failure in these four patients, oxygen inhalation and endotracheal suction were not adequate to prevent death, as indicated by cases 3 and 4. When there is a mechanical failure of the chest bellows the only effective therapy is the application of artificial respiration. In cases 1 and 2, artificial respiration was supplied by means of a Drinker respirator and maintained for 16 and seven days, respectively. The patients were followed with determinations of vital capacity, arterial oxygen saturation and blood carbon dioxide levels. Signs of acute infection, bronchial obstruction, atelectasis and swallowing difficulties were watched for constantly but did not appear. We remained continually prepared for emergency bronchoscopy and tracheotomy. The usual technics of respirator management and prophylactic chemotherapy were employed.<sup>6</sup> Our experience in being able to avoid tracheotomy in the two cases which made a complete recovery should not be construed as indicating that tracheotomy will not be necessary in similar cases in the future, especially those with evident bulbar dysfunction and accumulation of secretions.

Why many patients with acute multiple sclerosis make remarkable recoveries while others die has not been clarified in the literature. It has been speculated that fatal cases represent the outcome of an ascending paralysis during an encephalomyelitis. It is our impression that the fatalities in acute multiple sclerosis are a result of ventilatory failure caused by paralysis of the muscles of respiration. The use of a Drinker respirator was the deciding factor in maintaining the patient during the period of acute respiratory depression until there was an improvement in the neurologic status. Because of the tendency toward remission of acute attacks of multiple sclerosis, it is probable that deaths occurring during the acute illness may be prevented by the application of methods of treating ventilatory insufficiency.

The early recognition of ventilatory insufficiency is dependent upon measurements of vital capacity, blood oxygen saturation and blood carbon dioxide content. We advocate their use in the acute exacerbation of multiple sclerosis and, if there is evidence of ventilatory insufficiency, the early use of artificial respiration.

#### SUMMARY

1. Four cases of acute exacerbation of multiple sclerosis with respiratory insufficiency are presented, with two deaths.

2. In both of the fatal cases there was late recognition of ventilatory insufficiency, and treatment with oxygen and tracheal aspiration was not adequate to compensate for the paralysis of the muscles of respiration.

3. In both of the cases who lived, respiratory failure was recognized early, and they were managed in Drinker respirators for seven and 16 days, respectively.

4. Signs which should alert one to the possibility of respiratory insufficiency in multiple sclerosis are the rapid appearance of dyspnea, tachypnea, sensory defects in both upper extremities, or quadriparesis.

5. The measurements of vital capacity and arterial oxygen saturation are important in the early recognition of ventilatory failure in acute multiple sclerosis.

6. It is probable that many fatalities in the acute attack of multiple sclerosis are due to acute ventilatory insufficiency.

#### BIBLIOGRAPHY

1. Schumacher, G. A.: Multiple sclerosis, *J. A. M. A.* **143**: 1059 (July 22) 1950.
2. Marburg, O.: Die sogenannte "akute multiple Sklerose" (Encephalomyelitis periaxialis scleroticans), *Jahrb. f. Psychiat. u. Neurol.* **27**: 213, 1906.
3. (a) Riser Gérard, J., and Lavitry, S.: La sclérose en plaques aiguë, *Presse méd.* **46**: 1193 (Aug. 3) 1938.  
 (b) Marques, A.: Sobre la forma aguda de la ensclerosis en plaxas, *Rev. neurol. de Buenos Aires* **8**: 271 (July) 1943.  
 (c) Guillain, G., and Marquazy, R.: Le syndrome myéletique aiguë mode de terminaison de la sclérose en plaques, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**: 608, 1924.  
 (d) Ronne, H., and Wimmer, A.: Akute disseminierte Sklerose, *Deutsche Ztschr. f. Nervenhe.* **46**: 56, 1913.  
 (e) Rimbaud, L., Serre, H., Boucomont, J., and Godlowski, M.: Sclérose en plaques aiguë rapidement mortelle évoluant a un mois et demi d'intervalle chez deux soeurs: rôle probable de la contagion, *Rev. neurol.* **69**: 526 (May) 1938.  
 (f) Nielsen, J. M.: A textbook of clinical neurology, 3rd Ed., 1951, Paul B. Hoeber, Inc., New York.  
 (g) Merritt, H. H., and Wolf, A.: Clinical pathological conference, *Neurology* **2**: 161 (Mar.-Apr.) 1952.
4. Lichtenstein, B. W.: A textbook of neuropathology, 1949, W. B. Saunders Co., Philadelphia.
5. Von Storch, T. J. C., Lawyer, T., Jr., and Harris, A. H.: Colloidal gold reactions in multiple sclerosis, *Arch. Neurol. and Psychiat.* **64**: 668 (Nov.) 1950.
6. Plum, F., and Wolff, H. G.: Observations on acute poliomyelitis with respiratory insufficiency, *J. A. M. A.* **146**: 442 (June 2) 1951.

## AMYOTROPHIC LATERAL SCLEROSIS ON GUAM: A CLINICAL STUDY AND REVIEW OF THE LITERATURE\*

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THE purpose of this article is to report the unusual occurrence of an uncommon syndrome found in the native population of Guam. At the same time the American literature of the past 20 years has been reviewed to determine whether any notable differences could be demonstrated between the condition as found on Guam and as described in the literature.

Guam is an island of the Micronesian group, located about 13° above the equator in a climate where the temperature averages consistently about 85° F., and whose yearly rainfall averages about 80 inches. It is peopled by Chamorros whose original ancestry is reputed to be either Malayan or Polynesian. However, the people today are mainly intermixtures with Spanish and Filipino blood, and a few are of Chinese and Japanese ancestry. On the whole they work as farmers or laborers, and their diet consists largely of rice, tropical fruit, native vegetables, fish and, of late, imported canned goods.

The opportunity to study this group occurred during the author's assignment to the Guam Memorial Hospital as a naval medical officer. The patient population consisted chiefly of Guamanian natives, with a few natives from other island groups and a very few other nationals who made their homes on the island or were there in a transient status. Nevertheless, the condition was found only in the Guamanian patients. The unusual frequency of this disease was suggested by the admission of three cases within one month to the medical wards. Interest was further aroused by discussion of the condition with hospital personnel and by review of the hospital records. The following report was made possible only through the invaluable aid of Jose M. Torres,† who not only acted as interpreter when necessary in taking the history and conducting the physical examinations but also solved many of the nonmedical problems which arose during the study.

### METHOD

Our first step was to review 15,873 admissions to Guam Memorial Hospital since 1945, selecting all the cases suggesting anything involving the motor system. We then reviewed all the available charts of these cases.

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† Jose M. Torres was a member of the first graduating class of the School for Medical Assistants, conducted by the U. S. Navy for training in the medical sciences of natives from several Pacific islands, including American Samoa and the Marshall, Caroline and Marianas groups. J. Torres was the first to serve in the capacity of intern at the Guam Memorial Hospital.

obtaining 46 cases which appeared to be possible cases of amyotrophic lateral sclerosis. In like manner we reviewed 13,419 admissions to the adjacent U. S. Naval Hospital from July 1, 1947, to March 9, 1950, where the hospital population was comprised mainly of American military personnel and their dependents, civil service employees, many Filipino contract laborers and occasional other nationalities. It was of interest to find that over this period the diagnosis of amyotrophic lateral sclerosis was made in only two cases, and both of these were Guamanians in the naval service!

Thereupon, with our list of prospective cases, we went throughout the island, village by village, consulting in each place both the village commissioner and the native nurses in the local dispensary, asking, first, directions to the homes of patients on our list who were still living, and the dates of death of those who had died. At the same time we asked the names of anyone else in the village who was known to have similar symptoms or was "paralyzed." The natives tend to lump all conditions adversely affecting locomotion under the term "paralysis," which led to several cases of crippling arthritis, muscular dystrophy, residua of cerebrovascular accidents, and a case of multiple sclerosis. Although time-consuming, it had the effect of a fair screening process, giving us an idea of the incidence of other neurologic diseases prevalent on the island, and it brought out the fact that the cases of amyotrophic lateral sclerosis that we saw far outnumbered the combined total of the other neurologic conditions. The natives are well aware of the high incidence of the disease and also know that those patients who came to the hospital received little benefit. Therefore, it is conceivable that we may have missed an occasional case who had not sought medical aid and was not yet sufficiently incapacitated to have attracted the attention of his fellow villagers. The result of our survey was to examine 35 patients with the condition and to compile summaries of 16 others who had died before our arrival.

The patients visited lived in 15 villages scattered throughout the island. It was noted that two-thirds of the patients gave a common birthplace, the capital, which seemed of some epidemiologic interest. However, it was found on checking that the majority of the people had concentrated in the capital before the war, but when the city was leveled the inhabitants were forced to scatter to adjacent villages. In contrast to this group, the remaining third had been born and had remained in more remote villages which had been less disturbed by the war.

#### DESCRIPTION

Amyotrophic lateral sclerosis is a syndrome presenting signs and symptoms pointing to concomitant involvement of the new and old motor nervous systems. It is described as a clinical entity in the neurologic textbooks,<sup>1-6</sup> but most of the authors state that progressive spinal muscular atrophy, lateral sclerosis and progressive bulbar palsy may represent variants or anatomic

localizations of the same process. It is not difficult to consider the syndromes as due to the same process, proceeding at different paces and producing seemingly different pictures. Helfand<sup>9</sup> pointed out that he was unable to find any "pure" cases of progressive bulbar palsy in the literature from 1910 to 1933; and in the case he presented, with no clinical evidence of other system degeneration, he was able to describe classic changes in the anterior horn and motor cortex cells on histologic examination. Similarly, Spiller is quoted<sup>10</sup> as having found degenerating ventral horn cells at autopsy in six of his eight cases of clinical lateral sclerosis. Friedman and Freedman<sup>11</sup> described 12 cases of amyotrophic lateral sclerosis which had no clinical evidence of pyramidal tract disease, but postmortem findings revealed slight to extensive changes in these tracts. These findings suggest that morphologic changes may occur without giving clinical evidence of involvement, and that many patients may not survive long enough for clinical features of amyotrophic lateral sclerosis to evolve. It is also possible that amyotrophy may be so far advanced that signs of pyramidal tract involvement are masked. That amyotrophic lateral sclerosis itself may present a variable picture is evidenced by descriptions in the literature of monoplegic, hemiplegic and quadriplegic types.<sup>10-13</sup> Other classifications are made, e.g., cervical, lumbar and bulbar types, depending upon the location of the maximal involvement. Still other cases are described with initial involvement in the proximal muscles of the extremities rather than in the more classic site of the distal musculature.

#### INCIDENCE

The disease is so infrequently seen that nowhere is there to be found an estimate of its incidence among the general population. Friedman and Freedman<sup>11</sup> reported an incidence of 3.3 per cent among the neurologic admissions at their source of cases; Ziegler<sup>14</sup> reported 101 cases admitted to the Mayo Clinic over a five year span. Swank and Putnam<sup>10</sup> listed 151 cases admitted over a 10 year period at the Neurological Institute of New York. On Guam the situation was unique in that the entire population was accessible within the confines of the island, and we felt quite certain that we could have missed only the occasional case, if any, by our method of approach. We found an incidence of 13 cases per 10,000 inhabitants, based on a population of approximately 27,000 natives at that time. It is regrettable that hospital records before the war were not available for comparison but, as judged from conversation with the older natives, the condition seemed to be as prevalent before as after the war. The disease seemed localized to the island of Guam, since none of the students from the various Pacific isles at the School for Medical Assistants could recall having seen a similar case in their home islands. Likewise, the medical officer aboard a medical research ship which plied among the various islands accumulating medical data, etc., had not made the diagnosis among any of the patients he had seen.

## RACE

All races appear susceptible, although there are very few reports of the appearance of the disease in Orientals. Reed<sup>15</sup> in 1914 described one case and made the statement that the disease apparently was seen as often in the Chinese as in the Western world. In the past 20 years two case reports were found in the literature from China, one from Japan and one from India. Veit<sup>16</sup> reported a series of cases which included the first case reported in an Oriental in this country. As far as can be determined we believe our series is the largest to be reported among people of Oriental origin.

## AGE

The syndrome appears most frequently in middle life but can occur in almost any decade. Reed's<sup>15</sup> case is the youngest reported, with the onset at the age of 14. In our group the ages ranged between 26 and 69 years, with only seven outside the 30 to 50 year range, the average being 42 years.

## SEX

Males have been said to predominate in ratios varying from 2:1 to 4:1. Nineteen males and 16 females comprised our group.

## HEREDITY

It has been generally agreed that heredity plays no rôle in this disease, although there are sporadic reports in the literature in which there was some familial background. In this respect this series differs quite remarkably. Fourteen patients (40 per cent) gave a positive family history of one or more relatives who had the disease at the time of our survey or had died with it previously. One other patient gave a history that a sister had died of a slowly progressive "paralysis," but as we were unable to satisfy ourselves as to the true nature of the condition, it is not included in the statistics. Of the 14 patients with positive family histories we saw and verified seven cases, which included two brothers and a niece, two sisters, and a brother and sister. One case gave a history of four other siblings with the same condition, three cases had two other siblings similarly afflicted, and six had a single sibling with the disease. Although the genealogy of these cases is admittedly incomplete, chart 1 is an attempt to demonstrate the familial incidence in the various kindreds.

## ETIOLOGY

As is so often the case in diseases of unknown etiology, amyotrophic lateral sclerosis has been associated with conditions of multiple and varied natures.

1. *Stress*: Exposure, worry, exhaustion and disturbed emotional status are mentioned by several authors as at least possible contributing factors.

Ask-Upmark<sup>17</sup> expands this theory by suggesting that malnutrition may be a precipitating factor when superimposed upon conditions in which neuronal stress is already present, and to support this contention he cites five cases in which the syndrome appeared following disturbed digestion secondary to gastric resection. Certainly these Guamanians had adequate exposure to any or all of the above types of stress during the two and a half years of enemy occupation during World War II, together with faulty nutrition and perhaps also digestive or absorptive dysfunction secondary to parasitism, all leading to avitaminosis. Eighteen (51 per cent) of our group presented evidence of avitaminosis. Especially frequently seen was a conjunctival

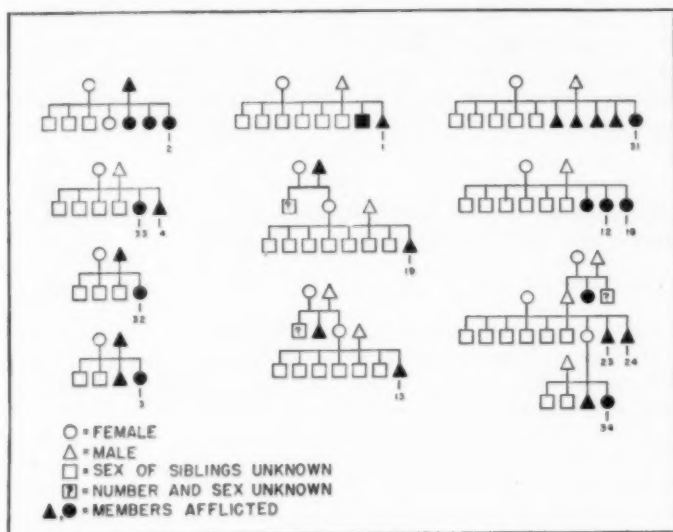


CHART 1. Familial incidence.

vascular overgrowth or proliferation, similar to that described in vitamin A deficiency. This latter, however, was frequently encountered among other natives without amyotrophic disease.

2. *Trauma*: Of all single factors suggested as possible precipitating causes, trauma has probably been mentioned most frequently. Jelliffe<sup>18</sup> summarized 90 cases from the literature in which the authors had noted a possible relationship to trauma. Critical review of these cases, however, reveals that any relationship is extremely doubtful in many of them. Alpers and Farmer<sup>19</sup> reported two cases in which patients had used pneumatic drills in their daily occupations and cited experimental evidence of production of progressive paralysis and degeneration of anterior horn cells by application

of blows over the spine or vibrations to the extremities of experimental animals. Having noted that transient vasomotor phenomena occur in the hands of people whose occupations expose these parts to repeated traumata of a vibratory nature, they suggest that the mechanism of this disease may be related to vasomotor influence. Veit<sup>10</sup> stated that three of his series showed indisputable evidence of a traumatic relationship. On the other hand, Waggoner and Löwenberg,<sup>20</sup> after reporting a case in which there was histologic evidence of amyotrophic lateral sclerosis and injury to the spinal cord without apparent relationship, refer first to the series of Starker and Cramer in which there was a traumatic incidence of 10 per cent and 11 per cent, respectively, then to 10 other authors who failed to reveal any definite relationship between injury and the neuropathologic lesions. Wechsler et al.<sup>12</sup> found none in their series with any traumatic history suggesting an etiologic relationship, and Swank and Putnam had only one patient in their group with associated trauma.

Only five patients in our series gave any history of trauma. One had received a shotgun wound in the shoulder 15 years before the onset of symptoms which appeared in the extremities of the opposite side. Another had received a severe concussion, with a period of unconsciousness for many hours, but this had occurred many years before the war. In neither of these was any possibility of relationship considered between the trauma and the disease. The remaining three had all received severe beatings at the hands of the enemy during the occupation, and symptoms appeared about four years later in two of them. The third stated that progressive weakness began in his lower arm soon after the beating, during which he lost consciousness several times, but other evidence of lower motor neurone disease and involvement of other parts did not occur until four years later.

3. *Inflammatory*: Ornstein,<sup>21</sup> in describing a case with onset after encephalitis, referred to the work of others, notably Wimmer, and Grinker and Carr, who had reported the appearance of amyotrophy after attacks of epidemic encephalitis. Swank and Putnam in their series had three cases with a history of encephalitis many years before the onset of the neurologic disorder. Neurosyphilis also has been associated fairly frequently with this condition, but these reports have appeared in most part in the European literature, with only a rare American report.

In reviewing the hospital records it was noted that there had been a sizable number of cases of encephalitis among the natives in 1945, and it was initially thought that this might have been significant, but at the conclusion of the survey none of the patients had given a history even suggestive of encephalitis during that period. One gave a history suggestive of encephalitis dating back 26 years before onset of his present symptoms, at which time many allegedly had died with similar manifestations of encephalitis. One other gave a history suggesting a meningoencephalitis following measles 23 years before the appearance of her symptoms. Venereal disease was seen ex-

tremely infrequently among the native population, and in this group no clinical evidence of syphilitic infection was found. Of the 11 patients seen in the hospital, two showed Kahn reactions of 4 plus and 2 plus, respectively. The spinal fluid Kahn was negative in both, and both were considered to have latent yaws, which was not uncommonly seen.

4. *Vascular Disease*: None of the patients in this series was known to have been diabetic. Among the general population it was uncommon to find disease secondary to arteriosclerosis, Buerger's disease or essential hypertension. In these patients evidence of minimal, uncomplicated arteriosclerosis was found in seven (20 per cent), and hypertension was found, surprisingly, in 11 (33 per cent). Most of the latter, however, were borderline hypertensives, barely exceeding 150 mm. of Hg systolic or 90 mm. diastolic pressure, but three were moderately advanced, the highest pressure recorded being 180/120 mm. of Hg.

5. *Miscellaneous*: Exposure to lead, gas fumes or heavy metals, and spinal anesthesia have been listed under toxic causes. None of these was elicited in any of the histories. Barnard and Friedland,<sup>22</sup> on the basis of the results of therapy with adrenal cortex in five patients with a strong personal and family history of allergy, advanced the theory that the etiology in at least some cases of amyotrophic lateral sclerosis may be on an atopic basis. For the sake of completeness it should be mentioned that amyotrophic lateral sclerosis, or a condition simulating it, has been described in isolated cases with other states or conditions<sup>23-25</sup> which probably were coexistent rather than of any etiologic import.

#### DURATION

Seven patients in this series succumbed during my stay on the island. In all cases the disease began with symptoms of spinal cord involvement ranging from eight to 41 months before death with an average duration of 22.4 months. Bulbar manifestations appeared from three to 35 months before death, averaging 13 months. Usable data were compiled from hospital records of nine other patients and the mortality statistics of the village commissioners. As listed in table 1, it appeared in the latter group that spinal symptoms occurred 10 to 24 months (average, 17) before death, and bulbar manifestations appeared five to 15 months (average, 10) before death. The shorter average period for spinal and bulbar symptoms in the latter group is explained in part by the unexpected death of one patient, and by another case which was complicated by advanced cirrhosis. Despite the usual short duration of the disease, some patients may survive for considerably longer periods, depending upon the localization and rapidity of progression of the disease. Two patients were living nine and seven years, respectively, from the onset of symptoms. The symptoms of the former were confined to the cord until only three months before our examination, when bulbar signs began to appear. In the latter case, however, symptoms of bulbar involvement appeared within one month of the onset of cord symptoms.

TABLE I  
Interval Between Symptom Onset and Death

	Spinal Symptoms	Bulbar Symptoms
A. Cases Seen		
1	18 mos.	4 mos.
2	8 mos.	4 mos.
3	18 mos.	3 mos.
4	41 mos.	35 mos.
5	30 mos.	12 mos.
6	18 mos.	16 mos.
7	24 mos.	17 mos.
Average	22.4 mos.	13 mos.
B. Cases from Hospital Records		
1*	10 mos.	8 mos.
2	14 mos.	?
3**	9 mos.	? duration
4	17 mos.	? duration
5	24 mos.	8 mos.
6	Early signs ? duration	5 mos.
7	17 mos.	13 mos.
8	20 mos.	15 mos.
9	24 mos.	?
Average	17 mos.	10 mos.

\* Advanced cirrhosis.

\*\* Sudden death.

# CLINICAL PICTURE

Classification as to types is purely arbitrary, based upon the region of the motor system predominantly affected at the time the examination was made (table 2). Six in our group could be classified as spinal types; five presented evidence of combined cervical and lumbar disease, and one had manifestations of cervical cord involvement only, but his symptoms were of only two months' duration. Four patients were predominantly bulbar in type, and the remaining 25 showed evidence of combined bulbar and spinal cord involvement.

## ONSET

The mode of onset was quite variable as to its nature and site of origin. The disease made its appearance most often in the upper extremities, starting there in 28 cases (80 per cent). However, as shown in table 3, in only 12 did it appear solely in the upper extremities. In 11 of the cases the legs were involved at the same time, in four bulbar symptoms were noted simultaneously, and in one case initial bulbar symptoms were accompanied by fibrilla-

TABLE II  
Classification of Cases

1. Spinal	6
A. Cervical	1
B. Combined cervical and lumbar	5
2. Bulbar	4
3. Combined bulbar and spinal	25

tions in all extremities. Three patients had initial complaints referable to bulbar involvement; dysarthria was the complaint of two, as it was in the four patients whose initial complaints indicated combined bulbar and spinal cord involvement. The remaining patient noted dysphagia at the onset of her disease. The lower extremities were affected first in four cases. Weakness and fibrillations, occurring together or individually, were the most common complaints. Pain never preceded other symptoms, but in three cases it accompanied weakness in one of the extremities involved in each instance.

#### NEUROLOGIC SIGNS

*A. Character and Distribution:* These varied, as might be expected, depending upon the duration of involvement and the rapidity of progression of the disease. As expected with lower motor neurone involvement, atrophy

TABLE III  
Initial Symptoms

1. Upper Extremities	12
A. Weakness and fibrillation	4
B. Weakness	2
C. Fibrillation	5
D. Atrophy	1
2. Lower Extremities	4
A. Weakness	3
B. Weakness and Fibrillation	1
3. Upper and Lower Extremities	11
A. Fibrillation	1
B. Weakness	2
C. Weakness and fibrillation	5
D. Pain in arm, weakness in legs	2
E. Weakness, fibrillation and atrophy	1
4. Bulbar	3
A. Dysarthria	2
B. Dysphagia	1
5. Bulbar and Upper Extremities	4
A. Dysarthria, weakness and fibrillation	1
B. Dysarthria, weakness, fibrillation and backache	1
C. Dysphagia, dysarthria, weakness and fibrillation	1
D. Dysarthria and weakness	1
6. Bulbar and All Extremities	
A. Dysphagia, dysarthria and generalized fibrillation	1

and fibrillation were very commonly noted, ranging from minimal involvement of the interossei to complete disability of an extremity due to extreme atrophy of the muscle groups involved. As is classically described, the atrophy occurred much more frequently in the upper extremities and, when present in the upper and lower limbs, was much more pronounced in the upper extremities. Even in the four cases in which weakness in the legs was the initial manifestation preceding upper extremity involvement by variable periods, atrophy in the legs was much less apparent than in the upper limbs affected for shorter periods. In three of these latter cases spasticity of the legs was a prominent finding. Muscular fibrillations were found present in distributions corresponding to that of the atrophy, and the frequency of the fibrillations in general paralleled the degree of atrophy.

*B. Upper Motor Neurone:*

1. Hyperreflexia was the most common, the earliest and occasionally the only sign suggesting corticospinal tract involvement. Only two cases failed to show this. One was a case of the bulbar type, with unilaterally absent abdominal reflexes and evidence of corticobulbar tract involvement. In the other, although hyperactive reflexes had been described in an earlier hospital admission, only a hyperactive ankle jerk and absent abdominal reflexes remained as evidence of pyramidal tract disease. The lower motor neurone involvement had become so extensive that it masked the signs of the higher system involvement. This latter case would have fitted better into the category of progressive muscular atrophy had not evidence of corticospinal tract disease been noted earlier.

2. Spasm or rigidity was noted in one or more extremities in 20 cases (57 per cent). The upper extremities were involved in 12 of these; but in only one instance was the upper extremity involved without concomitant involvement of the leg. Of the remaining cases with involvement of the upper extremity, eight showed bilateral spasm of the arm together with rigidity of the legs, in most cases the latter being more pronounced. One case demonstrated homolateral involvement, affecting both extremities to a similar degree. Two other cases showed both legs and only one upper extremity involved. Only eight cases had rigidity confined to the lower extremity, three being unilateral, the remainder bilateral in distribution. In two additional cases the gait tended to be somewhat spastic in the absence of rigidity on passive movement. In table 4 an attempt is made to correlate the pathologic reflexes, deep and superficial, and the degree of atrophy in cases exhibiting variable degrees of spasm.

3. Clonus, Babinski's and Hoffmann's Signs: In all but three of the cases exhibiting some degree of rigidity, one or more of these signs were present. Of these, one case was moribund, dying three days after the examination, but even she demonstrated some exaggeration of the patellar reflexes, with loss of abdominal reflexes in three of the four quadrants. The second demonstrated hyperreflexia in the presence of marked atrophy, with absent abdominal and cremasteric reflexes. The third was predominantly bulbar in type, with signs of corticobulbar tract involvement, whose reflexes were diminished with minimal early atrophy and unilateral loss of abdominal reflexes.

(a) Babinski Sign: This sign was unequivocally present at least unilaterally in 11 cases (31 per cent), all of whom demonstrated spasticity of the legs either on passive movement or on walking. In 10 cases of spasticity of the lower extremity the Babinski sign was negative; only in the three cases described earlier was this accompanied by absence of clonus. In the presence of moderate to marked atrophy in the legs the Babinski sign was positive in only two of six cases.

TABLE IV  
Correlation of Spasm, Atrophy, Pathologic, Deep Tendon and Superficial Reflexes

Extremities (Degree of Spasm)	Rabinak's R:L	Hoffmann's R:L	Clonus R:L	Degree of Atrophy	Biceps R:L	Triceps R:L	Patellar R:L	Achilles R:L	Abdominal	Cremas- teric
Upper (Unilateral)										
1. Slight (left)	7:0	++ +	0:0	Moderate of interosseal	2 +:3 +	3 +:2 +	4 +:4 +	2 +:3 +	Absent on left	
Lower (Unilateral)										
1. Slight (right)	0:0	0:0	s:u	Marked of upper ext.	4 +:4 +	4 +:4 +	4 +:4 +	4 +:4 +	Absent	
2. Moderate (left)	++ +	++?	s:s	Marked of upper ext.	4 +:4 +	4 +:4 +	4 +:4 +	3 +:3 +	Absent	
3. Moderate (right)	++ +	0:0	0:u	Marked of upper ext.	4 +:4 +	4 +:4 +	4 +:4 +	3 +:3 +	Normal	
Lower (Bilateral)										
1. Moderate	++ +	++ +	u:u	Marked of upper and lower	4 +:4 +	4 +:4 +	4 +:4 +	4 +:4 +	Normal	
2. Marked	0:0	0:0	0:0	Marked of upper and lower	0:3 +	0:0	4 +:4 +	2 +:2 +	Absent only in right RLQ	
3. Moderate*	0:0	0:0	0:0	Marked of upper and lower	0:0	0:0	3 +:4 +	2 +:2 +	Absent	
4. Slight	++ +	++ +	++ +	Moderate of upper ext.	4 +:4 +	2 +:2 +	4 +:4 +	4 +:4 +	Absent	
5. Marked	0:0	++ +	++ +	Rt. arm marked upper; mod- erate lower	4 +:0	4 +:4 +	3 +:3 +	3 +:3 +	Absent	
Lower and Upper (Combined)										
A. Quadriceps (upper and lower)										
1. Moderate upper, slight lower	0:0	0:0	0:0	Slight of interosseal	3 +:1 +	2 +:3 +	3 +:3 +	0:0	Absent on left	
2. Moderate upper, slight lower	0:0	++?	0:u	Marked upper	3 +:1 +	4 +:4 +	4 +:4 +	3 +:3 +	Decreased	
3. Slight upper and lower	0:0	++ +	u:s	Marked of upper and lower	3 +:1 +	3 +:4 +	4 +:4 +	3 +:3 +	Normal	
4. Marked upper and lower	++?	++ +	s:s	Marked of upper and lower	4 +:4 +	4 +:4 +	4 +:4 +	4 +:4 +	Decreased	
5. Slight upper and mod. lower	++?	++ +	s:s	Marked of upper and lower	4 +:4 +	4 +:4 +	4 +:4 +	4 +:4 +	Normal	
6. Moderate upper, marked lower	++ +	++ +	s:s	Marked upper	4 +:4 +	4 +:4 +	3 +:3 +	4 +:4 +	Absent on left	
7. Moderate upper, marked lower	++ +	++ +	0:0	Marked of upper and lower	4 +:4 +	0:0	3 +:3 +	2 +:2 +	Absent	
8. Marked upper and lower	0:0	0:0	0:0	Marked of upper and lower	4 +:4 +	0:0	4 +:4 +	2 +:2 +	Absent	
B. Hemiparetic										
1. Moderate in rt. arm and leg	0: +	++?	0:0	Moderate of interosseal	4 +:4 +	4 +:4 +	4 +:4 +	2 +:2 +	Normal	Decreased on left
C. Miscellaneous										
1. Marked both legs, slight rt. arm	++ +	++ +	s:s	Marked upper	2 +:2 +	4 +:4 +	4 +:4 +	4 +:4 +	Decreased	
2. Marked both legs, rt. shoulder	0:0	++?	s:s	Marked upper	4 +:4 +	4 +:4 +	4 +:4 +	4 +:4 +	Normal	

\* Terminal case.

† Bulbar type.

2 + Normal reflex.

u Sustained.

s Un sustained.

? Equivocal.

(b) *Hoffmann Sign*: This sign was positive in 13 cases (37 per cent), of which eight demonstrated some rigidity in the arms. Only one of the remaining failed to show any spasm in any of the extremities. In contrast to the Babinski sign in the presence of atrophy, the Hoffmann sign was found in nine of 16 cases of moderate to marked involvement of the upper extremities.

(c) *Clonus*: Ankle or patellar clonus or both were present in 17 cases (49 per cent), 14 of which demonstrated rigidity of the lower extremities. As indicated in table 5, clonus was found in seven cases in which the Babinski was negative and was absent in only two cases in which the latter was present. In one patient in whom clonus occurred in an arm; the Hoffmann sign was positive, and hyperreflexia was present on the affected side.

(d) *Superficial Reflexes*: The abdominal reflexes were absent in at least two quadrants in 16 cases (46 per cent). Of the six males included in this group, three had loss of the cremasterics. As has been noted by others, the superficial reflexes were frequently found to persist in extremely late stages of the disease. Of 15 cases who were completely bedridden and considered far advanced, the abdominal reflexes were present in eight. One of these, however, demonstrated loss of the cremasterics.

TABLE V

## Correlation of Spasm, Babinski's and Clonus

Rigidity or spasm in lower extremities	19
Spasm, Babinski's and clonus	7
Spasm and clonus only	7
Spasm and Babinski's only	2
Spasm alone	3

*C. Pseudo-bulbar Palsy Signs*: These findings constituted one of the unusual aspects of the series. Twenty-eight patients (80 per cent) had evidence of supranuclear lesions, as indicated by the eliciting of the sucking reflex or hyperactive jaw reflexes, or both combined with evidence of corticospinal tract and cranial nerve involvement. In 24 cases both the sucking and the jaw reflexes were elicited together, in three only a hyperactive jaw reflex was found, and in the remaining case the sucking reflex appeared alone. Of these patients, eight showed evidence of emotional instability.

*D. Cranial Nerves*: The hypoglossal was most frequently affected, 31 cases (89 per cent) presenting evidence of involvement. Of almost equal frequency, 30 cases (86 per cent) showed signs of ninth and tenth cranial nerve disease. The spinal accessory nerve was involved in a considerably greater percentage than has been described in the literature. Fourteen cases (40 per cent) showed weakness and atrophy of the trapezii or sternocleidomastoid muscles or both, in each case associated with disease of other bulbar nuclei. The motor division of the trigeminal was involved in six cases, and motor weakness of the seventh cranial nerve was detected in five.

## UNUSUAL FINDINGS

Sensory disturbances were described by 14 patients (40 per cent) as having occurred at some time during their illness. Paresthesias were noted by eight, pain by three, temperature discrepancies by two and muscular cramps by one. In no case were any objective signs of sensory change noted, although temperature perception was not tested. Sensory complaints have been recorded since the earliest literature, and some have found objective evidence of loss of sensation, Freedman and Friedman<sup>11</sup> reporting an incidence as high as 10 per cent in their series. Similarly, pathologic findings have been described in almost every sensory pathway,<sup>28-32</sup> but these changes were generally described as of relatively minor importance, and the subjective symptoms were far out of proportion to the objective abnormalities demonstrated.

Emotional disturbances such as forced or uncontrollable laughing or crying were described above in eight patients. No other evidence of personality changes or mental deterioration was found in this series. Psychosis together with amyotrophic lateral sclerosis has been reported rather sporadically in the literature,<sup>22, 33-36</sup> but no agreement has been reached as to whether the psychoses were coexistent with or represented sequelae of organic changes due to the same etiologic process as that of the amyotrophic disease.

Three cases showed fibrillatory movements in the eyelids, one of which presented other evidence of involvement of the facial nerve. Two others showed similar fibrillations without facial weakness but had associated involvement of other bulbar nuclei. It could not be ascertained whether these two cases represented early involvement of the fifth nucleus or whether the fibrillations originated farther out, near the periphery of the fifth nerve fibers. Work has been done<sup>26, 27</sup> showing that not all fibrillary muscle twitches arise centrally, and Davison<sup>28</sup> demonstrated that the pathologic process could be initiated at any point along the neurone.

Three patients became pregnant during the course of their illness, one subsequently delivering a nine pound, anencephalic monster. These cases are to be discussed in another report.<sup>37</sup> Large families were the rule, and of the 29 married patients in the series each had at least two children, the average for the group being nine offspring per married patient. There had been only three miscarriages among the 16 women.

Miscellaneous findings included sialorrhea in 11 patients, diplopia in five, without objective evidence of oculomotor dysfunction, and complaints of tinnitus or decreased auditory acuity in six cases, of which only one showed evidence of eighth nerve involvement.

## LABORATORY FINDINGS

Of the 12 patients on whom some laboratory data could be compiled, three showed some anemia, one hypochromic, two normochromic in type. Six had an eosinophilia greater than five cells, and parasites and ova were

found in the stools of three. Intestinal parasitism was common among the natives, and without a doubt positive stools would have been found in many more patients had a more diligent search been feasible during a longer period of hospitalization. The positive serologic reaction in two cases has already been discussed. The spinal fluid Kahn reaction and colloidal gold curves were normal in all cases tested. Spinal fluid protein exceeded 40 mg. per cent in only three cases, the highest being 48 mg. per cent.

#### TREATMENT

Specific treatment is no further advanced today than it was when Charcot first described the disease. Of the varied modes of medications, régimes, etc., vitamin E or tocopherol probably was hailed most enthusiastically. Certainly its use brought about a considerable conflict in the literature, many<sup>38-43</sup> seemingly obtaining beneficial results at least early in its use in amyotrophic lateral sclerosis. On the other hand, equally as many<sup>44-52</sup> obtained discouraging results. It is significant that of those reporting beneficial results, only Wechsler gave a follow-up report after a prolonged period. He had had no cures but claimed a few arrests, which helped lead him to the classification of the condition as primary or degenerative and secondary or symptomatic cases. In more recent years, Aird<sup>53</sup> reported modification or apparent arrest in a few cases with trypan red. Barnard<sup>54</sup> reported ameliorative results from administration of Tolserol. The latter also described some apparent benefit from adrenal cortex in three cases with history of hypersensitivity.<sup>22</sup>

#### SUMMARY

1. An unusual incidence of amyotrophic lateral sclerosis was found among the natives of Guam, and the disease seemed endemic to this Pacific isle. Thirty-five cases, or 13 per 10,000 inhabitants, were seen.
2. The literature for the past 20 years has been reviewed to determine if the condition on Guam differed in any way from that seen elsewhere.
3. An unusually high number of cases (40 per cent), gave a history of similar disease in other members of the family. As many as five members in one generation were afflicted.
4. No common etiologic factor could be demonstrated. The duration of the disease was similar to that reported elsewhere.
5. The clinical picture differed but little from that described classically. Some of the more unusual findings are given below: A. Spasm or rigidity occurred in seemingly more cases than have been previously described. Next to hyperreflexia it was the most common sign of upper motor neurone involvement. B. Clonus, absent superficial reflexes and Babinski's signs appeared next in order of frequency as indications of pyramidal tract disease. C. Signs of pseudobulbar palsy, as evidenced by hyperactive jaw reflexes and the sucking reflex, were found in an extremely large number (80 per

cent) of cases. D. The spinal accessory nerve was involved in 40 per cent, a figure considerably higher than is generally found in the literature.

6. Although all races appear susceptible, this seems to be the largest series of cases reported in people of Oriental origin.

#### BIBLIOGRAPHY

1. Grinker, R. R., and Bucy, P. C.: *Neurology*, 4th Ed., 1949, C. Thomas, Springfield, Ill.
2. Nielson, J. M.: *A textbook of clinical neurology*, 2nd Ed., 1947, Harper and Bros., New York and London.
3. Bing, R., and Haymaker, W.: *Textbook of nervous diseases*, 5th Ed., 1939, C. V. Mosby Co., St. Louis.
4. Wilson, S. A., and Bruce, A. N.: *Neurology*, The Williams and Wilkins Co., Baltimore.
5. Wechsler, I. S.: *A textbook of clinical neurology*, 5th Ed., 1943, W. B. Saunders Co., Philadelphia and London.
6. Jelliffe, S. E., and White, W. A.: *Diseases of the nervous system*, 5th Ed., 1935, Lea and Febiger, Philadelphia.
7. Walshe, F. M. R.: *Diseases of the nervous systems*, 2nd Ed., 1942, The Williams and Wilkins Co., Baltimore.
8. Alpers, B. J.: *Clinical neurology*, 1946, F. A. Davis, Philadelphia.
9. Helfand, M.: Progressive bulbar paralysis; the pathology and relation to amyotrophic lateral sclerosis, *J. Nerv. and Ment. Dis.* **70**: 362, 1933.
10. Swank, R. L., and Putnam, T. J.: Amyotrophic lateral sclerosis and related conditions; a clinical analysis, *Arch. Neurol. and Psychiat.* **49**: 151, 1943.
11. Friedman, A. P., and Freedman, D.: Amyotrophic lateral sclerosis, *J. Nerv. and Ment. Dis.* **111**: 1, 1950.
12. Wechsler, I. S., Sapirstein, M. R., and Stein, A.: Primary and symptomatic amyotrophic lateral sclerosis; a clinical study of 81 cases, *Am. J. M. Sc.* **208**: 70, 1944.
13. Pritchard, E. A. B.: Amyotrophic lateral sclerosis of unusual distribution, *Proc. Roy. Soc. Med.* **27**: 670, 1934.
14. Ziegler, L. H.: Psychotic and emotional phenomena associated with amyotrophic lateral sclerosis, *Arch. Neurol. and Psychiat.* **24**: 930, 1930.
15. Reed, A. C.: Nervous diseases in China, *Boston M. and S. J.* **171**: 638, 1914.
16. Veit, H.: Dynamic view of amyotrophic lateral sclerosis, *J. Nerv. and Ment. Dis.* **106**: 129, 1947.
17. Ask-Upmark, E.: Amyotrophic lateral sclerosis observed in five persons after gastric resection, *Gastroenterology* **15**: 257, 1950.
18. Jelliffe, S. E.: Amyotrophic lateral sclerosis syndrome and trauma, *J. Nerv. and Ment. Dis.* **82**: 415, 1935.
19. Alpers, B. J., and Farmer, R. A.: Role of repeated trauma by pneumatic drill in production of amyotrophic lateral sclerosis, *Arch. Neurol. and Psychiat.* **62**: 178, 1949.
20. Waggoner, R. W., and Löwenberg, K.: Role of trauma in amyotrophic lateral sclerosis, *Arch. Neurol. and Psychiat.* **45**: 296, 1941.
21. Ornstein, A. M.: The syndrome of amyotrophic lateral sclerosis in epidemic encephalitis, *J. Nerv. and Ment. Dis.* **72**: 369, 1930.
22. Barnard, R. D., and Friedland, S.: The atopic nature of amyotrophic lateral sclerosis: evidence afforded by results with adrenal cortex therapy, *New York State J. Med.* **50**: 1365, 1950.
23. McCullagh, E. P., and Hewlett, J. S.: Acromegaly associated with amyotrophic lateral sclerosis and acromegaly of the amyotrophic type, *J. Clin. Endocrinol.* **7**: 636, 1947.
24. Young, R. H.: Syndrome of amyotrophic lateral sclerosis of bulbar type associated with platybasia, *J. Nerv. and Ment. Dis.* **97**: 133, 1943.

25. Kayne, G. G.: Retrosternal goitre and amyotrophic lateral sclerosis, *Proc. Roy. Soc. Med.* **26**: 524, 1933.
26. Swank, R. L., and Price, J. C.: Fascicular muscle twitches in amyotrophic lateral sclerosis; their origin, *Arch. Neurol. and Psychiat.* **49**: 22, 1943.
27. Shelden, C. H., and Woltman, H. W.: Origin of fibrillary twitches, *Proc. Staff Meet., Mayo Clin.* **15**: 646, 1940.
28. Davison, C.: Amyotrophic lateral sclerosis. Origin and extent of the upper motor neuron lesion, *Arch. Neurol. and Psychiat.* **46**: 1039, 1941.
29. Davison, C., and Wechsler, I. S.: Amyotrophic lateral sclerosis with involvement of posterior column and sensory disturbances, clinicopathological study, *Arch. Neurol. and Psychiat.* **35**: 229, 1936.
30. Wohlfart, S., and Swank, R. L.: Pathology of amyotrophic lateral sclerosis. Fiber analysis of the ventral roots and pyramidal tracts of the spinal cord, *Arch. Neurol. and Psychiat.* **46**: 783, 1941.
31. Hassin, G. B.: Amyotrophic lateral sclerosis. Anatomic and pathologic considerations, *Arch. Neurol. and Psychiat.* **43**: 765, 1940.
32. Hassin, G. B.: Amyotrophic lateral sclerosis, complicated by sub-acute combined degeneration of the cord; clinical and pathological report of a case, *Arch. Neurol. and Psychiat.* **29**: 125, 1933.
33. Friedlander, J. W., and Kesert, B. H.: The role of psychosis in amyotrophic lateral sclerosis, *J. Nerv. and Ment. Dis.* **107**: 243, 1948.
34. Wechsler, I. S., and Davison, C.: Amyotrophic lateral sclerosis with mental symptoms; a clinicopathological study, *Arch. Neurol. and Psychiat.* **27**: 859, 1932.
35. Androp, S.: Amyotrophic lateral sclerosis with psychosis, *Psychiatric Quart.* **14**: 818, 1940.
36. Meller, C.: Amyotrophic lateral sclerosis with psychosis, paranoid type, *Minnesota Med.* **23**: 858, 1940.
37. Lingenfelder, J. L.: Personal communication.
38. Wechsler, I. S.: Recovery in amyotrophic lateral sclerosis treated with tocopherols (vitamin E), preliminary report, *J. A. M. A.* **114**: 948, 1940.
39. Rosenberger, A. I.: Observations on the treatment of amyotrophic lateral sclerosis with vitamin E, *M. Rec.* **154**: 97, 1941.
40. Bicknell, F.: Vitamin E in the treatment of muscular dystrophies and nervous diseases, *Lancet* **1**: 10, 1940.
41. Davison, C.: Effect of vitamin E therapy on the central nervous system in amyotrophic lateral sclerosis, *Bull. New York Acad. Med.* **19**: 386, 1943.
42. Weinberg, M. H., and Knoll, A. F.: Beneficial effect of vitamin E on amyotrophic lateral sclerosis, *M. Rec.* **152**: 447, 1940.
43. Weber, J. J., and Clinco, A. A.: Report of a case of amyotrophic lateral sclerosis treated with vitamin E, *M. Times, New York* **70**: 247, 1942.
44. Lubin, A. J.: Use of alpha tocopherol in treatment of neuromuscular disorders, *Arch. Int. Med.* **69**: 836, 1942.
45. Merwarth, H. R.: Synthetic vitamin E in the treatment of amyotrophic lateral sclerosis and related disorders, *Dis. Nerv. System* **2**: 325, 1941.
46. Eaton, L. M., Woltman, H. W., and Butt, H. R.: Vitamins E and B<sub>12</sub> in the treatment of neuromuscular disease, *Proc. Staff Meet., Mayo Clin.* **16**: 523, 1941.
47. DeJong, R. N.: Vitamin E and alpha tocopherol therapy of neuromuscular and muscular disorders, *Arch. Neurol. and Psychiat.* **45**: 1068, 1941.
48. Denker, P. G., and Scheinman, L.: Treatment of amyotrophic lateral sclerosis with vitamin E (alpha tocopherol), *J. A. M. A.* **116**: 1893, 1941.
49. Ferrebee, J. W., Klingman, W. O., and Frantz, A. M.: Vitamin E and vitamin B<sub>12</sub> in the treatment of muscular dystrophy and amyotrophic lateral sclerosis, clinical experience, *J. A. M. A.* **116**: 1895, 1941.

50. Doyle, A. M., and Merritt, H. H.: Vitamin therapy of diseases of the neuromuscular apparatus, *Arch. Neurol. and Psychiat.* **45**: 672, 1941.
51. Schwarz, G. A., Gammon, G. D., and Masland, R. L.: Use of d-1 alpha tocopherol acetate (synthetic vitamin E) in various neuromuscular disturbances, *J. Nerv. and Ment. Dis.* **96**: 286, 1942.
52. Zech, V. L., and Telford, I. R.: Negative effect of massive doses of vitamin E on amyotrophic lateral sclerosis, *Arch. Neurol. and Psychiat.* **50**: 190, 1943.
53. Aird, R. B.: Trypan red therapy of amyotrophic lateral sclerosis, preliminary report, *Arch. Neurol. and Psychiat.* **59**: 779, 1948.
54. Barnard, R. D.: Rectal administration of tolserol: the therapeutic efficiency of this route as demonstrated in amyotrophic lateral sclerosis, *New York State J. Med.* **49**: 2190, 1949.

## ALCOHOL-OXYGEN VAPOR THERAPY OF PULMONARY EDEMA: RESULTS IN FIFTY ATTACKS \*

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THE numerous measures used in the treatment of acute pulmonary edema (A.P.E.) attest to the fact that no therapy is consistently satisfactory and generally useful in this syndrome. Although reliable statistics of incidence and prognosis in pulmonary edema are unavailable, the condition is widely observed and is frequently followed by death. As previously pointed out,<sup>1-4</sup> all conventional therapeutic measures, i.e., morphine and other hypnotics, oxygen under positive pressure, mercurials, venesection, etc., may be harmful in certain cases.

A new method of treatment, utilizing the anti-foaming action of alcohol vapor, was successfully tried in animal experimentation by one of us.<sup>1</sup> Following this study, Luisada, Goldmann and Weyl<sup>2,3,4</sup> reported on the use of ethanol-oxygen vapor (E.O.V.) in normal subjects, cardiac patients, and 17 patients suffering from pulmonary edema associated with a variety of diseases. Other workers have published two cases suggesting confirmation of these conclusions.<sup>5</sup> The purpose of the present report is to analyze the result of a more extensive experience with this mode of treatment.

### SELECTION AND TYPE OF CASES

Early in the course of this study, it was recognized that a statistical comparison between a control group of patients treated with conventional methods and another treated with E.O.V. would be desirable but misleading. Differences in age, sex, general physical status and underlying etiologic factors, variability in severity and duration of attacks, and the necessity of depending upon the judgment of various physicians in an experiment embracing hundreds of patients, would shed considerable doubt on the statistical validity of such a comparison. Therefore, an objective and detailed study was made of each patient who was the subject of a request for E.O.V. therapy by a responsible member of the house staffs. This plan served to exclude attacks that were mild or undergoing spontaneous recovery. E.O.V. was never administered to patients who showed evidence of improvement under other management.

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Detailed observations relative to history, physical findings, laboratory investigations and prior therapy were made. The severity of each attack was graded as follows: mild, 1 plus; moderate, 2 plus; severe, 3 plus; and extremely severe, 4 plus. With the exception of two cases of moderate severity (2 plus), all attacks studied were of severe (3 plus) or extremely severe (4 plus) intensity. Many of the 4 plus attacks were among the most fulminating ever observed in these hospitals.

TABLE I  
Age of Patients with Acute Pulmonary Edema

20-29	30-39	40-49	50-59	60-69	70-79	Total
1	1	4	8	9	12	35 cases (40 attacks)

Over a period of more than 18 months, E.O.V. by inhalation was administered to 45 patients for 50 attacks. Forty of the attacks were paroxysmal, and 10 were of a protracted nature. The latter group will be discussed separately. Twenty of the patients with paroxysmal attacks of A.P.E. were males and 15 were females. As shown in table 1, all but two of the patients studied were over 40 years of age, and 60 per cent were over 60 years of age.

The patients treated for A.P.E. are classified according to primary diagnosis as follows:

<i>Hypertensive Cardiovascular Disease</i> .....	18
With coronary heart disease .....	6 (2 with diabetes)
With pregnancy at term .....	1
With chronic glomerulonephritis and uremia .....	1
With coarctation of aorta .....	1
Others .....	9
<i>Coronary Heart Disease</i> .....	8
With acute myocardial infarction .....	3
Others .....	5
<i>Cerebrovascular Accident</i> .....	5
With hypertensive C-V disease .....	3
(1 also had coronary heart disease)	
With bronchogenic carcinoma .....	1
Others .....	1
<i>Postoperative</i> .....	2
With hemolytic transfusion reaction .....	1
With coronary heart disease .....	1
<i>Rheumatic Valvular Disease</i> .....	1
<i>Syphilitic Heart Disease</i> .....	1

#### METHOD OF ADMINISTRATION

Three methods of administration of E.O.V. by inhalation were used.

*Nasal Catheter:* This method was employed in 72 per cent of the attacks (36). A nasal catheter is placed in the patient's nasopharynx in the usual manner. Oxygen is obtained from conventional equipment, consisting of a tank, adjustable pressure regulator, flowmeter and vaporizer (humidifier). Treatment is initiated with ethanol (ethyl alcohol) in the vaporizer replacing

the water usually contained in it. The flow of oxygen is started slowly (2 to 3 L. per minute), and the tubing adapter is connected to the nasal catheter. Within five to seven minutes the oxygen flow is progressively raised to 7 or even 10 L. per minute, as tolerated. Usually this rate is maintained throughout the course of therapy.

It is recommended that 95 per cent ethanol be used in the vaporizer; however, if this concentration is unavailable, 70 per cent ethanol, although less desirable, may be substituted. Any humidifier that promotes good vaporization may be used. The model 15 Ohio-Heidbrink or the Airco type was found satisfactory. Although less efficient, a urine specimen bottle with a two-hole stopper, holding a long tube to deliver the oxygen into the alcohol and a short one to remove the vapor, may be used. It should be noted that the amount of alcohol vaporized will vary directly with the rate of oxygen flow and the efficiency of the atomizer.

*Mask:* A mask, with or without positive pressure, may be used in place of the nasal catheter with the above described equipment. When this is done, 30 to 40 per cent ethanol should be used in the humidifier, since higher concentrations are usually not well tolerated. A mask may also be used with standard equipment for gas anesthesia, and 30 per cent ethanol placed in the "ether" container. Although generally not so practical, the last mentioned technic is most convenient when an emergency arises in the operating or delivery room. For obvious reasons, any technic involving the use of a mask is less desirable in the conscious, apprehensive patient; moreover, it impairs his ability to expectorate the fluid resulting from liquefaction of foam. On the other hand, it is the most suitable in the unconscious patient.

*Tent:* Five patients were treated by diffusing ethanol vapor into a closed tent. Since this method was found less efficient, and made the environment uncomfortable for the patient, it was abandoned. In this series, the nasal catheter technic was tolerated well by two patients after poor toleration of the tent and mask technics, respectively.

#### EVALUATION OF RESPONSE TO THERAPY

Since pulmonary edema is usually only one aspect of a complex morbid condition and not the sole determinant of mortality, survival cannot be taken as the critical measure of therapeutic success. Pulmonary edema may persist following treatment and yet the patient may rally subsequently. Even though death occurring during an attack can usually be ascribed to A.P.E., it may also take place hours or days later following definite improvement of A.P.E. and be the result of the underlying disease (e.g., myocardial infarction, uremia, etc.). For this reason detailed information was collected as to (a) duration of A.P.E. prior to therapy, (b) conventional measures administered prior to the use of E.O.V. and the time at which given, (c) degree of improvement following other measures, (d) duration and toleration of ethanol therapy, and (e) time of maximal benefit and total duration of

therapy. Observations were made as to general condition before and after therapy: changes in blood pressure, pulse and respiration, and objective pulmonary findings. Roentgenograms of the chest, electrocardiograms and other pertinent tests were obtained when feasible.

The subjective and objective evidence of improvement occurring during treatment is of the greatest cogency. In addition to the patient's testimony, a change from unconsciousness to consciousness, from labored to more normal respiration, from inability to speak to ability even to hold the breath, a slowing of the pulse, reduction of cyanosis, decrease in quantity and liquefaction of the expectorate, and decrease in the number and extent of pulmonary râles (or their disappearance) were accepted as evidence of improvement. Both subjective and objective improvement were separately classified from 0 to 4 plus. Only complete or practically complete recovery was considered as 4 plus.

#### RESULTS OF THERAPY IN ACUTE PULMONARY EDEMA

The patients were divided into four groups:

1. E.O.V. used exclusively.
2. E.O.V. used after oxygen.
3. E.O.V. used after adequate and unsuccessful trial of other conventional measures.
4. E.O.V. used after failure to improve with other measures, but when the waning action of other drugs could not be absolutely discounted.

*Ethanol and Oxygen Exclusively:* Following casual demonstration that E.O.V. per se induced recovery in severe attacks of A.P.E., a larger group of patients, selected at random, was treated without additional therapeutic measures. It should be understood that other therapy was withheld only because improvement progressed satisfactorily with E.O.V.

A total of 14 attacks was treated exclusively with ethanol and oxygen by inhalation. In all attacks but one, 95 per cent ethanol and a nasal catheter were used. Three attacks were very severe, nine severe, and two of moderate severity.

In nine attacks, no prior therapy for A.P.E. had been given. The other five had been uninfluenced by oxygen alone when E.O.V. was started. In a sense, the exposure to oxygen without positive pressure served as a control for the period during which ethanol was added to the system, although actually, bubbling the gas through ethanol has the effect of reducing the pressure of oxygen delivered to the patient at a given rate of flow. It is worthy of emphasis that the general condition of the patients in this group was classified as poor to terminal in all but one instance.

*All 14 attacks so treated definitely responded to E.O.V. therapy, and moreover, improvement was maintained after its discontinuance.* Maximal benefit was obtained in one hour or less in all but two attacks. Improvement was excellent or complete—frequently dramatically so—in 85 per cent of this

group (12 attacks). In the remaining 15 per cent (two attacks), improvement occurred but was not marked. In one of the latter, all subsequent measures were without avail.

#### CASE REPORTS \*

*Case 1.* A 50 year old white female with hypertensive cardiovascular disease was semicomatose and unimproved one hour and a half following the onset of A.P.E. of 4 plus severity. Ninety-five per cent E.O.V. was administered by nasal catheter and dramatic improvement ensued. Forty-five minutes after therapy was begun, improvement was 4 plus subjectively and objectively. Therapy was discontinued after two hours and 15 minutes. No other treatment for A.P.E. was given. The patient was later discharged to the Cardiac Clinic.

*Case 2.* A 53 year old Negro male with severe dyspnea and thoracic pain was expectorating frothy bloody sputum on admission. A.P.E. of 4 plus severity was present. Ninety-five per cent E.O.V. was administered by nasal catheter. Within 30 minutes improvement was definite. After one hour the therapy was discontinued. The patient was able to lie flat comfortably, and only minimal basal râles were present. Improvement was classified as 4 plus subjectively and 3 plus objectively. A diagnosis of acute myocardial infarction was confirmed by electrocardiogram. The patient absconded eight days after admission.

*Case 3.* A 65 year old white female with A.P.E. of 3 plus severity and of three hours' duration was treated in the hospital. Oxygen by mask for 30 minutes had failed to induce improvement and no other treatment had been given. Within 30 minutes of institution of 95 per cent E.O.V. by nasal catheter, improvement was 3 to 4 plus subjectively, and 3 plus objectively. Toleration of the vapor was good. After 45 minutes, treatment was discontinued. A diagnosis of hypertensive cardiovascular disease, class III, with left ventricular hypertrophy, was established. After convalescence, the patient was discharged to the Cardiac Clinic.

*E.O.V. after Failure of Conventional Measures:* Twenty-three attacks of A.P.E. were treated with E.O.V. after other treatment definitely failed to induce improvement. Thirteen of these attacks were very severe, nine were severe, and one was of moderate severity. The general condition of all these patients was classified as poor or very poor. In 17 instances, E.O.V. was instituted well after conventional measures could have been expected to exert a therapeutic effect. *E.O.V. inhalation was followed by objective improvement in 15 (88 per cent) of these attacks.* Maximal improvement occurred within an hour in all but one, so that recovery was prompt and complete, or almost so, in 12 (71 per cent) of this group.

In six other attacks, conventional measures were without avail, but their waning effect could not be completely discounted during the period of E.O.V. inhalation. The results were similar: all six improved and five of them were completely recovered, or markedly improved, within one hour.

*Case 4.* A 65 year old white female with coronary heart disease and calcific aortic stenosis suffered a posterior myocardial infarction and developed shock and A.P.E. of 4 plus severity. Morphine sulfate, 15 mg., atropine sulfate, 1.2 mg., and desoxyn, 10 mg., were administered intravenously. Notwithstanding these measures, her blood pressure dropped to 70/60 mm. of Hg. Ninety minutes later the patient

\*None of the cases described herein was previously reported. Three detailed descriptions of attacks responding dramatically to E.O.V. appeared in an earlier publication.<sup>4</sup>

was considered in agony and 40 per cent E.O.V. was administered by mask. Tolerant was apparently good. Improvement was gradual and progressive, being 4 plus subjectively and objectively at the end of six and one-half hours. After eight and one-half hours, ethanol therapy was discontinued. The patient was discharged four weeks later.

*Case 5.* A 73 year old white female with hypertensive cardiovascular disease and A.P.E. of 3 plus severity was unimproved following the administration of morphine sulfate, 30 mg. hypodermically, and oxygen by mask over a period of three hours and 20 minutes. Mercuhydrin, 2 c.c. intramuscularly, was administered one hour and 40 minutes before ethanol-oxygen therapy, without amelioration. After 30 minutes of 30 per cent E.O.V. by mask, the patient was able to expectorate, and improvement (4 plus subjectively and 3 plus objectively) was noted. Tolerant of the vapor was good. Some basal râles remained for 12 hours, but the patient's subsequent course was uneventful.

Three attacks did not lend themselves well to the above classification. In one of these, the responsible physician administered morphine sulfate hypodermically 10 minutes after E.O.V. had produced definite improvement, although the drug was probably not required. A second patient improved on E.O.V. but suffered a relapse after 400 c.c. of 25 per cent glucose were administered intravenously. Subsequent E.O.V. produced some improvement but, even after venesection, the patient's condition deteriorated and he died four hours later. A third patient strenuously objected to 30 per cent E.O.V. per mask, and therapy was discontinued after a 10 minute trial without evidence of improvement.

We observed only one patient (case 6) who responded to another mode of therapy after E.O.V. completely failed to mitigate the pulmonary edema. It is notable that such classic measures as morphine and oxygen were equally unsuccessful, and that only venesection induced recovery.

*Case 6.* A 38 year old white female had a hemolytic transfusion reaction and developed A.P.E. of 4 plus severity following the intravenous administration of 4,800 c.c. of blood, saline and glucose during and after abdominal surgery complicated by shock. Two hours after fluids were stopped, positive pressure oxygen by mask and morphine (first 5 mg. intravenously, then 10 mg. hypodermically were given) without avail. Fifty minutes later, 95 per cent E.O.V. was introduced into the mask apparatus (without trained supervision). It was poorly tolerated, and could only be used intermittently. Over the next three hours no improvement occurred, and the patient remained comatose. The mask technic was then abandoned and 95 per cent E.O.V. was administered by nasal catheter for one and one-half hours, without improvement other than rise of blood pressure to normotensive levels. At this point tourniquets were placed on the lower extremities, 600 c.c. of blood were removed by venesection, and morphine sulfate, 8 mg., was repeated intravenously. Within 15 to 20 minutes definite subjective and objective improvement was noted, and subsequently the chest cleared. The patient's surgical convalescence has been protracted.

A summary of subjective and objective results in the various categories of treatment appears in table 2.

The over-all mortality in patients with A.P.E. was seven deaths in 35 patients with 40 attacks. Five of the seven patients who died were clinically relieved of pulmonary edema but subsequently died of other causes.

TABLE II  
Results of Ethanol-Oxygen Vapor Therapy in A.P.E.

Mode of Therapy	Attacks Treated		Improvement		
	Degree of Severity	Total	Degree	Subjective	Objective
Oxygen and ethanol only	++++ 3 +++ 9 ++ 2	14	++++ +++ ++ ? 0	43% 22% 7% 28% none	21% 64% 15% none none
E.O.V. given after failure of other procedures	++++11 +++ 5 ++ 1	17	++++ +++ ++ ? 0	35% 30% 12% 12% 11%	30% 41% 18% none 11%
Possible contributory action of other procedures	++++ 3 +++ 6 ++ 0	9	++++ +++ ++ ? 0	33.3% 33.3% none 33.3% none	16.6% 66.8% 16.6% none none
All methods	++++17 +++20 ++ 3	40*	++++ +++ ++ ? 0	38% 28% 7% 20% 7%	28% 50% 15% none 7%

Severity of attacks graded as follows:

++++ very severe  
+++ severe  
++ moderate

Improvement graded as follows:

++++ complete or almost complete  
+++ good  
++ fair  
? patient unable to render judgment  
0 none

\* One of the patients tolerated therapy poorly for only 10 minutes.

#### "SUBACUTE" PULMONARY EDEMA: RESULTS OF THERAPY

While symptoms and signs of pulmonary edema in its paroxysmal form are well recognized, a less dramatic variant is more insidious in onset, has a protracted course and is less likely, per se, to be the crucial issue for the prognosis. In the absence of any established nomenclature, this form was designated as subacute pulmonary edema.

Although results of therapy in subacute pulmonary edema are even more difficult to evaluate than in the acute form, 10 such patients were studied. Five were 70 years of age or older and all were in a very poor or terminal state when E.O.V. therapy was initiated. None was considered likely to survive. Classified according to primary diagnosis, they were:

Myocardial infarction .....	3
Coronary heart disease (with failure) .....	2
Postoperative complications .....	2
Malignant nephrosclerosis (with uremia) .....	1
Massive pneumonia and anemia .....	1
Cerebral thrombosis (with encephalomalacia) .....	1

Pulmonary edema was severe in five of these attacks and moderate in the other five. Seven patients were benefited by E.O.V., but in two of these the effect was minimal (1 plus). Improvement was moderate (2 plus) in two, and good (3 plus) in three. Of the seven patients who benefited from therapy, six subsequently died, since E.O.V. failed to reverse the fatal course of the underlying condition (see above classification). In general, improvement was neither so prompt nor so marked as in the group with A.P.E. Illustrative case summaries follow:

*Case 7.* A 77 year old white male with coronary heart disease and probable anterior myocardial infarction developed pulmonary edema of 3 plus severity over a period of at least 14 hours. His general condition was considered extremely poor. Ninety-five per cent E.O.V. was administered by nasal catheter, and after 35 minutes of therapy 3 plus objective improvement was manifest. Thereafter, the patient removed the nasal catheter only to suffer a relapse. Another course of E.O.V. returned him to his earlier improved state. Subsequently, his condition deteriorated and he died two days later, without pulmonary edema.

*Case 8.* A 65 year old white male with coronary heart disease and congestive failure gradually and progressively (over a period of 15 hours) developed pulmonary edema of 3 plus severity. Nasal oxygen, morphine sulfate 15 mg. hypodermically, aminophylline 0.25 gm., and 3 units of Digalen intravenously, were given without avail. Ninety-five per cent E.O.V. administered into a closed tent was tolerated poorly and was abandoned. Ninety-five per cent E.O.V. was started by nasal catheter and improvement was 3 plus (objectively) 20 minutes later. After 40 minutes of therapy, improvement was so well established that E.O.V. was discontinued. The patient died suddenly on the following morning. Autopsy revealed a recent antero-septal infarction and marked left ventricular hypertrophy, but no froth in the tracheo-bronchial tree.

#### TOLERATION OF E.O.V. BY INHALATION

Ethanol-oxygen vapor was well tolerated in 47 (or 92.5 per cent) of the attacks studied. Toleration was fair in one patient and poor in another treated with 30 per cent ethanol and nasal catheter. Excellent toleration in normal subjects and cardiac patients without pulmonary edema has previously been reported.<sup>4</sup> One patient with malignant hypertension and uremia tolerated 95 per cent E.O.V. by nasal catheter for 12.5 hours without complaint or evidence of deleterious effect.

The following clinical experiment was performed to observe directly the effect of E.O.V. on the pulmonary mucosa. A 63 year old white male, bronchoscoped because of hilar calcification of undetermined etiology and found to have a normal tracheobronchial tree, was given 95 per cent E.O.V. per nasal catheter. Oxygen flow was brought to 6.5 L. per minute over a period of 15 minutes, and maintained at that rate until one hour of therapy was completed. During E.O.V. inhalation blood pressure remained con-

stant, and pulse and respirations did not change significantly. There was evidence of cutaneous vasodilatation at 15 minutes, and the patient expectorated two or three times during the treatment. Subjectively, the patient's only comment was that the vapor helped him to "clear" his "throat." On the third day the patient was again bronchoscoped, and the same examiner rendered the opinion that the tracheobronchial tree remained unchanged and absolutely normal. The bronchoscopist had not been informed of the nature or of the anticipated results of the experiment. Since a tracheobronchial tree bathed in fluid should be more resistant than the normal to the local effect of drugs, it is even less likely that E.O.V. therapy would produce undesirable local changes during A.P.E. This experiment objectively corroborates the clinical impression that E.O.V. is free of local deleterious effects in the amount given.

E.O.V. was administered to one case of bronchial asthma (status asthmaticus of many hours' duration) without deleterious effect and, surprisingly enough, with an excellent result.

#### MODE OF ACTION

The antifoaming action of ethanol vapor has been demonstrated *in vitro* and in animals.<sup>1</sup> A similar action is evident in the liquefaction of expectorate that was observed in many of the patients reported herein. The low alcohol concentrations \* and the relatively minor general effects observed in normal patients receiving E.O.V. by inhalation indicate that the benefits of this therapy are due primarily to its local antifoaming action. In severe pulmonary edema one can expect that absorption of inspired vapor will be reduced to even lower levels, other factors being equal. This view is also supported by the fact that much higher blood levels are required for a beneficial effect in animals with experimental pulmonary edema when alcohol is given intravenously than when it is given by inhalation.

Nevertheless, the importance of such factors as moderate peripheral vasodilatation and mild central sedation, as seen within the first half-hour of therapy in several of our patients, cannot be completely discounted. The successful use of E.O.V. in a case of bronchial asthma (where foam is not a significant factor) and the disappearance of wheezes associated with the other signs common in A.P.E. rouse speculation as to a possible direct or indirect relaxing effect on the tracheobronchial tree, in addition to the other factors mentioned.

#### COMMENT

In general, severe attacks respond most dramatically and those of shorter duration recover more promptly as a result of E.O.V. therapy. Usually,

\* Serum alcohol concentration less than 10 mg. per cent in two normal adults after 30 minutes of inhalation from standard gas anesthesia apparatus with 95 per cent ethanol in vaporizer; 19 mg. per cent in a normal adult after 30 minutes of 95 per cent E.O.V. administered by nasal catheter. (Most conservative limit for safe operation of motor vehicles is 50 mg. per cent.\*)

subjective relief precedes objective improvement. Frequently the patient feels that recovery is complete while some râles may still be heard in his chest.

No contraindication to the use of E.O.V. was found in this large heterogeneous group of patients with diverse underlying disease. A.P.E. resulting from exposure to irritating gases presents a special problem not represented in this series, and therefore, we must reserve judgment relative to toleration of E.O.V. in this condition.

It has been shown in patients under treatment with tetraethylthiuram disulfide (TETD) that the maximal safe concentration of alcohol by inhalation is less than one third that tolerated by other individuals.<sup>6</sup> Blood concentration of 20 to 30 mg. per cent can result in severe reactions in these persons. Since prolonged E.O.V. therapy may induce blood levels of this order, pretreatment with TETD contraindicates the use of E.O.V.

The smarting of the nasopharynx that sometimes occurs when E.O.V. is initiated does not persist for more than 5 to 10 minutes, at which time a local anesthetic effect is probably established. Such irritation may be avoided or minimized by starting the oxygen flow gradually, as outlined above. In the patient who is very uncoöperative, preliminary sedation may be used, although this was unnecessary in the 45 patients reported.

The same safety precautions as are customary with simple oxygen should be taken when E.O.V. is being administered.

#### SUMMARY AND CONCLUSIONS

The results of ethyl alcohol-oxygen therapy by inhalation in clinical cases of pulmonary edema are reported. This therapy was based on previous experimental and clinical studies indicating the beneficial action of an anti-foaming agent directly acting within the tracheobronchial tree.

Three methods of administration were studied but only two were considered satisfactory. That employing a nasal catheter and 95 per cent alcohol is the most suitable for conscious patients and was used in 36 attacks. That employing a mask and 30 to 40 per cent alcohol is more convenient in unconscious patients and was used in the others. Details of technic are given.

Ethyl alcohol by inhalation was used in 50 attacks presented by 45 patients. Forty attacks were acute, 10 subacute. Selection of cases and evaluation of results are discussed.

Ethyl alcohol vapor and oxygen by inhalation were used exclusively in 14 attacks. An excellent result, frequently with dramatic improvement, was noted in 12 (85 per cent). Maximal benefit usually occurred within an hour.

Ethyl alcohol-oxygen vapor was used after failure of conventional therapy in 23 attacks (13 very severe, nine severe, one moderate). Objective improvement occurred in 15 (promptly in 12 of them). Six other attacks responded similarly, but a waning effect of previous therapy could not be altogether discounted.

Over-all mortality in cases with acute pulmonary edema was 7 deaths among 35 patients with 40 attacks, 5 of whom were clinically relieved of the edema well before death.

Subacute or protracted pulmonary edema is defined. Ten cases presenting this clinical picture were treated. Improvement was good in three, moderate in two, and minimal in two, while the other three failed to improve. Six of these patients died subsequently because of the underlying condition.

Toleration of this new method of therapy was found excellent in 47 out of 50 attacks. Bronchoscopy failed to reveal untoward local changes in one case. In control subjects, minimal absorption of alcohol was revealed by blood determination. Contraindications are discussed.

Ethyl alcohol by inhalation has been considered the method of choice in patients with shock (including coronary patients), in central nervous system lesions, and in pregnancy. Since it can be used in conjunction with other measures and frequently succeeds where other procedures fail, this method should be given an extensive trial in all cases of acute pulmonary edema and in selected cases of subacute pulmonary edema.

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#### BIBLIOGRAPHY

1. Luisada, A. A.: Therapy of paroxysmal pulmonary edema by antifoaming agents, *Circulation* 2: 872, 1950.
2. Luisada, A. A., Goldmann, M. A., and Weyl, R.: Read by title before Annual Session of American Heart Association, June, 1951.
3. Luisada, A. A., Goldmann, M. A., and Weyl, R.: Therapy of acute pulmonary edema by antifoaming agents, Exhibit before Graduate Fortnight, The New York Academy of Medicine, October, 1951.
4. Luisada, A. A., Goldmann, M. A., and Weyl, R.: Alcohol vapor by inhalation in the treatment of acute pulmonary edema, *Circulation* 5: 363, 1952.
5. Gootnick, A., Lipson, H. I., and Turbin, J.: Inhalation of ethyl alcohol for pulmonary edema, *New England J. Med.* 245: 842, 1951.
6. Lester, D., and Greenberg, L. A.: The inhalation of ethyl alcohol by man, *Quart. J. Stud. on Alcohol* 12: 167, 1951.

## LIFE STRESS, EMOTIONS AND PAINFUL STIFF SHOULDER \*

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### INTRODUCTION

THE common complaint of pain and stiffness in the shoulder or adjacent bodily structures often presents a complex diagnostic and therapeutic problem. In the introduction to a symposium devoted to this subject, Young made the following comment: "In order to make an accurate diagnosis of the various lesions that may cause pain in the arm and shoulder, he (the physician) should have some knowledge of orthopedics, neurology, cardiology, and of diseases of the abdomen, thorax and blood vessels."<sup>23</sup> This would imply that with such specialized knowledge the basis for the symptom of painful shoulder can be readily established. Unfortunately, such is not always the case. Often even the most comprehensive physical and laboratory examination does not reveal the etiology of this syndrome. Meyerding and Ivins, for example, were unable to ascertain a causative factor in 72 per cent of 150 consecutive cases of stiff, painful shoulder.<sup>16</sup> Chronic trivial trauma or wear and tear are considered by many to be the major cause of subacromial bursitis or tenonitis of the musculotendinous cuff of the humerus.<sup>3, 6, 8, 15</sup> Yet, even here, others have observed that more often than not the etiology is obscure.<sup>2, 5, 9, 19</sup> In only seven of 41 cases of acute calcified bursitis reported by Bosworth was there a clear-cut history of trauma.<sup>1</sup>

Recently we have been impressed with the frequency of complaints referable to the shoulder region in emotionally ill patients. It is well known that the musculoskeletal system often is involved in the somatic expression of emotionally conditioned disorders,<sup>10, 12, 14, 18, 20, 22</sup> and the importance of emotions and life stress to tension headache, low backache, generalized muscular aching (myalgia), tremors and tics is quite well documented and generally accepted. The possibility that pain and stiffness in the shoulder area might also be emotionally conditioned, and another form of musculoskeletal somatization reaction, seemed worthy of investigation.

### MATERIAL AND METHODS

In 300 medical patients seen in consultation because they had various psychosomatic disorders, (1) the frequency of pain and stiffness of the shoulder and adjacent bodily structures was determined; (2) the nature of these symptoms was investigated by appropriate clinical and laboratory

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study, and (3) the relationship between the onset and course of such complaints and the patient's emotional disturbance and reactions to life stress was evaluated. Each subject in the group had a complete medical history, thorough physical examination and indicated laboratory procedures, including hemogram, sedimentation rate, serologic reaction, blood chemistry determinations, urinalysis and roentgenogram of the chest.

During psychosomatic consultation a fairly detailed life history was obtained, and particular note was made of the relationship between stressful life situations, emotional conflicts and fluctuations in the patient's state of health, both past and present. In addition, each was appraised psychologically, so that an impression of his basic personality traits, emotional stability, degree of maturity and general level of life adjustment could be formulated.

In the instances in which complaints referable to the shoulder region were not spontaneous, the patients were questioned directly regarding the presence of such symptoms. If denied, no further effort was made to establish their occurrence. In all cases presenting shoulder complaints, possible "organic" causes were investigated by obtaining indicated studies such as roentgenograms of the shoulder, cervical and dorsal spine, spinal fluid examination, oil myelography, and electrocardiogram. In addition, many of the patients were seen in consultation by specialists in orthopedics, neurology, neurosurgery or physical medicine.

#### RESULTS

1. *Incidence, Sex and Age:* Sixty patients, representing 20 per cent of the total number examined, complained of pain and stiffness in the shoulder region. Thirty-six were females and 24 were males. The age ranged from 25 to 55 years, with the largest number in the fourth decade.

2. *Chief Complaint:* Approximately two thirds of the 60 patients presented a chief complaint of "pain in the chest," "pain in the shoulder" or "pain in the neck." When pain in the chest predominated, accompanying pain or aching and stiffness in the shoulder and arm were usually present. In the remainder the presenting symptom was "nervousness," "headache," "fatigue," "muscle aching" or "rheumatism," but discomfort and disability referable to the shoulder region were prominent among the secondary complaints. The majority had experienced shoulder symptoms for two or three years, a few had had them for only three or four weeks, and five had had them for as long as five or more years.

3. *System Review and Secondary Symptoms:* Systemic review revealed the presence of a rather stereotyped pattern of symptoms. Although few had all of the following, the majority had most of them: (1) "headache," usually of the muscle tension variety but occasionally migrainous in type; (2) chronic "nose trouble"—vasomotor rhinitis, allergic rhinitis, frequent "colds," etc.; (3) "nervousness," defined by anxiety, tenseness, restlessness, irritability, insomnia, etc.; (4) "weakness"—easy fatigue, morning asthenia; (5) "dizzy spells"; (6) "stomach trouble," as manifested by flatulence,

pyrosis, postprandial abdominal discomfort, morning anorexia or nausea, and constipation (five patients had a past history of peptic ulcer); (7) "heart trouble," as evidenced by exertional dyspnea, palpitation, tachycardia or angina-like pain, and (8) muscular discomfort, such as migratory aching, recurrent nocturnal cramps or "restless legs."

Without exception, one or more of these groups of symptoms preceded the development of shoulder complaints by a period of from several months to several years. Their nature suggested the presence of quite long-standing emotional difficulties in these patients.<sup>17</sup>

4. *Physical and Laboratory Examinations:* The general physical findings in the group were quite unremarkable. All of them were tense and prone to over-react to physical stimuli. Generalized skeletal muscle hypertonus was prominent. Signs of autonomic instability, such as cold and clammy hands and feet, excessive sweating, dilated pupils and sinus arrhythmia, were noted frequently. Hyperventilation was common and in some instances was associated with aggravation of symptoms. A few had mild essential hypertension.

The left shoulder was involved in 34 patients, the right in 16, and both in 10. In the affected shoulder, when the arm was internally rotated and flexed behind the back, palpation over the greater tubercle of the humerus (in the region of the supraspinatus tendon and subacromial bursa) produced marked discomfort and frequently exquisite pain. Likewise, palpation of the adjacent pectoralis muscles was painful. The site of maximal pectoral tenderness very often corresponded to the location of the patient's thoracic pain. To a lesser extent, tenderness of the upper portion of the trapezius and the latissimus dorsi muscles was noted. Quite often, there was some degree of limitation of motion at the shoulder, especially in abduction and internal rotation. There was a tendency on the part of most patients to "protect" the painful shoulder by elevating the shoulder girdle on the affected side and by holding the arm close to the chest. This physical attitude resulted in relative disuse of the extremity and probably contributed to contracture of shoulder musculature. Occasionally, crepitation within the shoulder joint was demonstrated on passive motion of the arm.

The physical findings referable to the shoulder were, in the majority of patients, compatible with a diagnosis of subacromial bursitis, tenonitis of the musculotendinous cuff of the humerus, or contracted shoulder. In the absence of more definitive diagnostic criteria, an impression of "painful stiff shoulder" or "tension shoulder syndrome" was made.

With the exception of five patients, in whom calcification in the supraspinatus tendon or subacromial bursa was demonstrated, roentgenograms of the shoulder were normal. In a few cases, mild decalcification of the bones forming the shoulder and some evidence of soft tissue contracture were noted. The electrocardiograms were normal except in one instance, where changes were present which suggested early coronary insufficiency. All other laboratory studies were noncontributory.

5. *Relationship of Symptoms to Life Stress:* With few exceptions, pain and stiffness in the shoulder or adjacent bodily structures occurred in a setting which was emotionally stressful for the patients. These coincident environmental or interpersonal situations seemed neither unique nor specific, yet within the group they tended to be quite similar.

Circumstances resulting in an increase in responsibility beyond the patient's emotional limitations frequently preceded the onset of symptoms. In some instances this resulted from the unexpected loss of a strong supporting figure or the death of a marital partner. In others it was brought about by the assumption of additional duties and activities which eventually proved to be difficult and unpleasant. Characteristically, these patients were unable to reorganize their daily routines successfully or alter their work patterns to accommodate their increased burdens. Support and assistance were not available. In spite of this, they sought to "carry on" in a determined and sometimes desperate manner in an effort to attain their established goals. When they found themselves unable to accomplish their objectives satisfactorily or to resolve their problems effectively, there was progressive increase in their psychomotor activity. Soon thereafter, pain and stiffness in the shoulder region appeared. In some, these symptoms served as a legitimate excuse for giving up. More often, the patient doggedly persisted in his efforts in spite of growing anxiety over health and physical adequacy. Such hypochondriacal fears were particularly common in patients whose stressful life situations involved the cardiac death of a relative, marital partner or close associate. Here the appearance of pain in the left chest, usually associated with activity, and accompanied by pain in the shoulder and arm, had ominous cardiac implications. With the addition of dyspnea, palpitation, weakness and easy fatigue, anxiety and fear of sudden death increased. At this stage, iatrogenic factors frequently crystallized the patient's conviction of the presence of heart disease.

Twelve subjects attributed their shoulder symptoms to some specific physical effort or injury. Objectively, the amount of trauma seemed trivial, and it was difficult even for the patient to accept it as the sole cause of his disability. When careful inquiry was made into all of the circumstances attending the "injury," it became obvious that the setting in which it occurred was an emotionally stressful one. Seldom, however, had the emotional factors spontaneously been recognized as being related in any way to the trauma and development of symptoms.

In general, the course of a patient's shoulder discomfort and disability roughly paralleled his day-to-day emotional reactions. When he was permitted to "let down," was relieved of responsibilities, or was pleasantly diverted for a while, he improved symptomatically. When he was particularly frustrated or faced with an unusually unpleasant problem, he became more uncomfortable. Pleasant and recreational activities commonly were accomplished with much more ease than unpleasant and monotonous duties, even though they required equal or greater expenditure of physical energy.

6. *Personality Pattern and Attitude:* Although no uniformity in environmental situation or specific type of life stress was found to be related to the occurrence of symptoms in this group, their attitudes toward their life situations and the manner in which they reacted to them were remarkably similar. Likewise, they had a number of personality traits in common. Basically, they were (1) aggressive-dependent, (2) obsessive-compulsive, (3) "hyperkinetic," and (4) resentful. The combination of these characteristics seemed to be of fundamental importance to the rather stereotyped attitude and pattern of bodily response manifested by these patients under stressful circumstances.

With few exceptions, these individuals considered themselves as quite independent, self-sufficient and energetic "doers." The vast majority were serious, restrained, overly conscientious, and unusually rigid in their convictions and pattern of living. Beneath this façade their inherent insecurity and dependence were reflected in the excessive worry, anxiety and tension which appeared when their perfectionistic standards could not be maintained. Most of them were easily annoyed and impatient. They undertook their responsibilities with unusual aggressiveness and determination and permitted themselves few diversions as long as a task remained to be finished. Gradually, in the face of what seemed excessive odds, determination gave way to growing feelings of frustration, discouragement and futility, particularly when strong emotional support and continual reassurance from others, which they needed to help them persevere in their efforts to succeed, were not forthcoming.

A measure of the abundant aggression shown by these individuals found an outlet in their performance of work and expenditure of physical energy. The remainder was expressed by deep-seated feelings of resentment. They were unable, or unwilling because of their standards, to express openly and directly hostile-aggressive feelings, and they continually "had to struggle" to control or restrain such impulses. Overburdened with unpleasant responsibilities, they felt themselves the victims of circumstances beyond their control and certainly not of their choosing. The very existence of the situation was resented intensely, just as were the various factors which seemed to conspire to produce it. Yet to them there was no solution but to "shoulder the burden and carry on."

#### CASE REPORTS

*Case 1.* A 33 year old widow.

*Chief Complaint:* "Pain in the joints and shoulders."

Two years prior to hospitalization, while caring for her husband who was dying of cancer, the patient became aware of increasing ease of fatigue and aching in the muscles of the extremities and occasionally in the joints. Following his death, which left her with a 14 year old son and a variety store to manage, her pain localized in the back of the neck and shoulders. It was made worse by elevation of the arms. Movement of this type was also associated with a "shocklike" sensation radiating into

the fingers. At times she was aware of a "clicking" in the shoulder joints with movement. Various types of medication had been ineffective.

By systems, the patient complained of weakness, marked fatigue upon arising in the morning, frequent occipital and vertical headaches, shortness of breath with excitement, menstrual irregularity and severe insomnia.

Upon examination the patient appeared worn, tired and very tense. No significant abnormalities other than those relating to the shoulders were present. The blood pressure was 114/70 mm. of Hg. Motion at both shoulders, particularly abduction and internal rotation, was somewhat limited, particularly on the left. The pectoralis muscles were tender and hypertonic. Palpation over the region of the tendon of the supraspinatus muscle and subacromial bursa caused severe pain.

Routine laboratory studies were normal, as was the electrocardiogram. Roentgenogram of the shoulders demonstrated a calcareous density in the region of the subacromial bursa or supraspinatus tendon on the left, as well as bilateral soft tissue contractures.

The patient had always been a perfectionistic, obsessive-compulsive person who had struggled to maintain high standards which she would not compromise. She had been deeply attached to and very dependent upon her husband, whose death she had never accepted. She was reluctant to consider herself as a "widow," and expressed much criticism of such people as a group. She stated that she was completely "numb" after her husband's death and that she could not and would not allow herself to cry. She prided herself in her ability to "fight worry" and to control herself emotionally. She had dedicated herself to hard work to "forget the death of my husband." In continuing the operation of the store she had been required to handle considerable stock, some of which was heavy. The business had not gone well. In addition, she had found the needs of her home and the growing demands of her son very trying. She had felt an increasing sense of futility in the fulfillment of her responsibilities and had become more and more bitter over the unfortunate events in her life.

*Case 2. A 43 year old married male.*

*Chief Complaint: "Pain in joints."*

In 1947, while on strike, the patient had noted an aching pain in the right thigh, followed in one week by pain and stiffness in the right shoulder. These symptoms gradually subsided, but two months later similar disability in the left shoulder appeared and was soon followed by exacerbation of the symptoms on the right. Use of the right upper extremity became difficult and on frequent occasions there was aching in the joints of the fingers. Various types of therapy failed to provide relief. Recurrent migratory chest pains which increased with deep breathing appeared. All symptoms were relieved by alcohol and aggravated by excitement and fatigue.

By systems the patient complained of blurred vision, tightness in the back of the neck, nervousness, irritability and insomnia. A peptic ulcer had been diagnosed 10 years before.

Upon examination the patient appeared to be in good general health. He was very apprehensive and excessively tense. The hands and feet were cold and clammy. No arthritic changes were present. There was, however, considerable tenderness of skeletal muscles. Motion at the right shoulder, particularly abduction and internal rotation, was limited, and there was tenderness of the right trapezius and pectoralis muscles. Palpation over the region of the tendon of the supraspinatus muscle and subacromial bursa was exquisitely painful. The remainder of the physical examination was entirely normal.

Routine laboratory studies, electrocardiogram and roentgenograms of the shoulders were normal.

The patient was found to be an insecure, hard-working and easily dissatisfied

person. He characterized himself as one "who could never leave a task undone," and in the face of obstacles which interfered with his accomplishment of an objective he became irritated and angry. During the above noted strike, which lasted five months, he became disgruntled with his trade union, but since he had already alienated himself with management he felt himself trapped in a situation over which he had no control. He was convinced his employers were "out to get him," and he considered every irregularity in his assignments as an indication of this. A similar paranoid trend was reflected in many of his interpersonal relationships. He expressed deep resentment toward the treatment he had received. His attitude toward his life situation was one of hostility and aggressiveness which he struggled to restrain. He continually had a "chip on his shoulder."

*Case 3. A 42 year old widow.*

*Chief Complaint: "Pain in the chest."*

Approximately 18 months before hospitalization the patient had noted the onset of weakness and an aching pain in the left side of the chest, aggravated by deep breathing. Shortly thereafter she suffered an episode of severe, sharp pain in the left chest which lasted for approximately one hour. This recurred two days later. As it subsided there was residual pain and stiffness in the left arm, which increased with movement. This had persisted to the time of admission.

For many years the patient had suffered from frequent frontal headaches, occasionally accompanied by vomiting, recurrent dizziness, frequent colds, constipation, flatulence, pyrosis, multiple food idiosyncrasies, and recurrent vague abdominal pain. She felt she was very susceptible to upper respiratory infections. Her present illness had been accompanied by severe weakness, excessive morning fatigue, nervousness and insomnia.

The patient's husband had died of a cerebral vascular accident five years before, leaving her with the total responsibility for rearing their three children. One sister suffered from severe heart disease.

Upon examination the patient appeared to be in good general health. There was moderate seborrheic dermatitis. The blood pressure was 110/70 mm. of Hg. Passive movements of the left arm at the shoulder caused pain. There was tenderness and some mild contracture of the left pectoralis muscle. Voluntary hyperventilation was accompanied by thoracic pain, dizziness, trembling and weakness.

The patient was an insecure, rather dependent and emotionally unstable person. She had reacted with prolonged vomiting during her three pregnancies and had been slow in regaining her strength after each delivery. Over the years her recurrent gastrointestinal symptoms and headaches had fluctuated with the severity of the stress of her life situations. Six years prior to hospitalization her husband's poor health and inability to provide for the family had made it necessary for her to obtain work in a factory. Shortly thereafter, recurrent attacks of dizziness and weakness appeared. Following the death of her husband several months later she suffered a reactive depression of moderate severity. She then maintained a reasonably good life adjustment until her eldest daughter, whom she had hoped would soon be able to go to work and assume some of the responsibility for supporting the family, ran away from home. The patient reacted to this with considerable resentment and depression, yet she "struggled to carry on." It was in this setting that her chest and shoulder symptoms appeared.

*Case 4. A 41 year old married male.*

*Chief Complaint: "Chest pains."*

The patient stated that he had not been well for approximately 10 years. Initially, and coincident with an increase in occupational stress, he had developed a "nervous stomach" characterized by flatulence, recurrent nausea, occasional vomiting, colicky abdominal pain and intermittent bouts of diarrhea. In addition, he experienced easy

fatigue and became more irritable. During approximately 18 months of military service his symptoms grew more severe. He became "very nervous" and easily annoyed. Shortly after his discharge, an older brother had a "heart attack" and died. One month later the veteran began to experience recurrent sharp, "shocklike," migratory pains in the chest. These occurred approximately twice weekly and at any time of the day or night without relationship to activity. Ease of fatigue had become more marked. He also experienced listlessness, morning asthenia and rather frequent spells of sweating, flushing, tremulousness and dryness of the mouth. A frontal headache was commonly present on arising in the morning. Dizziness occurred with exertion. The patient stated that he could "belch for hours at a time when doing heavy work."

Upon examination the patient appeared to be in good health. The hands and feet were cold and clammy. Axillary sweating was excessive. He swallowed air frequently. The blood pressure was 130/80 mm. of Hg. The pectoralis muscles were very tender and hypertonic. Palpation in the region of the left subacromial bursa caused severe pain.

Routine laboratory studies were normal. Electrocardiographic changes were those of vasomotor instability. A roentgenogram of the shoulders was negative.

The patient was a very tense, hyperactive and aggressive-dependent person. He complained bitterly about his many responsibilities and the excessive work he was required to do. On the job his foreman had been a continual source of annoyance to him. He stated that "when I'm around him it is all I can do to keep from blowing my stack." He worried over his inability to provide adequately for his family, and stated: "No matter how hard I work I can't make both ends meet." In earlier years he had relied heavily upon his brother for encouragement and assistance. The brother's death had been a "shock" to the patient from which he had "never recovered." He had come to feel that he too suffered from heart disease, and that because he was unable to restrict his physical activities he would eventually die as his brother had. He saw no solution to his problems and felt helpless in the face of them.

*Case 5.* A 37 year old married female.

*Chief Complaint:* "Pain in the chest."

Five months prior to admission this patient experienced the abrupt onset of left thoracic pain, dyspnea, palpitation, weakness, dizziness and "numb aching" of the left arm and hand. These symptoms first appeared while she was sitting at home a few hours after helping her husband push their stalled car. The local physician suspected "angina," but the patient was not hospitalized with this diagnosis until after a second "attack" the following day.

Physical examination at that time was not remarkable. Repeated electrocardiograms were within normal limits. She promptly improved. Approximately one week later, while still hospitalized, she developed typical symptoms and signs of thrombophlebitis in the left calf. The sedimentation rate was 42 mm./hour. After six days of anticoagulant therapy there was complete remission of symptoms, and the patient was discharged.

There was, however, a prompt recurrence of "cardiac" complaints, and the patient was referred to the University Hospitals with a primary diagnosis of "coronary insufficiency." An additional consideration was recurrent hyperthyroidism, since the patient had had thyrotoxicosis proved, and then treated, by I<sup>131</sup> three years previously, shortly after her first and only pregnancy. The possibility of cardiac neurosis was mentioned.

System review revealed the presence of occipital headaches, "neckache," frequent choking sensations, chronic constipation, gaseousness, intolerance to fried and fatty foods, "nervousness" and low backache.

On examination the patient appeared healthy. She was somewhat obese and ob-

viously excessively tense. Her hands and feet were cool and damp. The deep reflexes were hyperactive. The blood pressure was 120/70 mm. of Hg. Cardiac examination was normal. There was marked tenderness on firm palpation over the tendon of the supraspinatus muscle in the region of the subacromial bursa. The trapezius and pectoral muscles on the left were tense and tender. Point pressure on the left pectoral muscle in the region of the patient's "heart pain" produced marked pain similar to that experienced during her "heart attacks." Hyperventilation for less than two minutes reproduced many of the other "attack" symptoms, including numbness and aching in the left arm.

Routine laboratory studies were normal, as were the serum cholesterol, basal metabolic rate and electrocardiogram. A roentgenogram of the left shoulder was negative.

The patient recognized that she had "always been nervous," rather "hot tempered," "easily hurt" and quite perfectionistic. She was also aware of the rôle of emotions in her long standing gastrointestinal symptoms. Her pregnancy three years before was unplanned and unwanted. The patient had mixed feelings about her growing son. He was a frequent source of anxiety and annoyance, especially in relation to his "nervous" overactivity and "demanding nature." The patient was constantly fearful lest some harm or fatal illness befall the boy, and she tended to overprotect and "pamper" him. Her husband had grown progressively demanding yet negligent in his "husbandly" duties, which was intensely resented but never directly expressed by the patient. Under these circumstances the patient had turned more and more to her overly sympathetic parents for solace and advice. Eight months prior to the patient's present illness her father had had a "heart attack" while visiting her and had subsequently died. The patient's mother had a "coronary thrombosis" two months thereafter. It was a few days after visiting her mother and while preparing to go on a vacation trip by car with her family that the patient's first "attack" occurred. She admitted being reluctant to leave her mother before she was entirely well and recalled having a premonition that "something terrible was going to happen" if she did.

#### DISCUSSION

The data derived from this study lend support to the initial consideration, that pain and stiffness in the shoulder area may be emotionally conditioned and another form of musculoskeletal somatization reaction.

It is recognized that the 300 patients who provided the basis for this study were a select group and thus not necessarily representative of the patient population in general. It does not follow, however, that this detracts from the importance and significance of the recorded observations. The recognition that pectoral girdle symptoms are of frequent occurrence in patients suffering from emotional disorders, and the realization that this bodily reaction pattern may have a particularly dire meaning to these individuals, have obvious diagnostic and therapeutic value. Furthermore, these observations may be relevant to that large percentage of patients having painful stiff shoulder or subacromial bursitis hitherto classified as being of "obscure etiology." Emotional and situational factors are not revealed by even the most careful physical and laboratory examinations. The inability of earlier investigators to establish a clear-cut and comprehensive etiology for this syndrome in many patients may be a consequence of the limitations imposed by their methods of evaluation. It would seem prudent for future

studies to be so conducted as to permit evaluation of psychic as well as somatic factors in the pathogenesis of painful stiff shoulder.

The consistency with which a stereotyped pattern of secondary symptoms occurred in these patients with shoulder complaints suggests that this may be used as a diagnostic aid. In the patient not obviously emotionally disturbed who complains primarily of pain and stiffness in the shoulder area, the presence of this pattern of secondary symptoms may serve as a clue to the clinician that further evaluation of emotional factors is indicated, particularly if subsequent physical and laboratory examinations are not revealing.

It is noteworthy in this regard that demonstration of aberrant calcification in roentgenograms of the shoulder seemed to have no bearing on the severity of symptoms, physical findings or degree of disability in this group of patients. Nor did the presence of such "organic" disease in the tissues serve as a differential point against the significant rôle played by emotions and life stress in the pathogenesis of painful stiff shoulder.

The importance of sustained excessive muscle tension associated with chronic emotional disturbances in the production of somatic symptoms has been shown experimentally. Anxious individuals with pain in the head and neck or backache have increased electromyographic potentials in the skeletal muscles of the involved area.<sup>6,10</sup> Malmö and co-workers found that emotional stress was accompanied by increased muscular tension in the site to which symptoms were referred.<sup>13</sup> Jacobson has written extensively concerning the importance of "neuromuscular hypertension" in various psychoneurotic states.<sup>12</sup>

Within skeletal muscle, tone is maintained by the alternating contraction and relaxation of different groups of muscle fibers in relays.<sup>11</sup> This is effected by a continuous flow of asynchronous nerve impulses from reflex centers in the spinal cord to the various motor units comprising the muscle. Impulses arising in cerebellar, brain stem and cortical centers are capable of profoundly altering the degree of tonus. Upon the institution of voluntary muscular effort, the existing tonus pattern must be overcome and the increasing flow of impulses to the motor units synchronized. Stetson and Bouman have shown that the effectiveness of muscle contraction depends not only upon the number of functioning motor units and increased frequency of impulses, but also upon the extent to which the nerve impulses are synchronized.<sup>21</sup>

The patients in this study who had pain and stiffness in the shoulder area were uniformly rigid, insecure, resentful and hyperkinetic. In addition, they exhibited a characteristic pattern of dealing with stressful life situations in which they vigorously and relentlessly attacked their problems despite what seemed to them to be insurmountable difficulties. Psychologically, these individuals were engaged in a continual struggle between their dependent needs and restrained resentment on the one hand, and their aggressive drives

on the other. Physically, in a somewhat analogous manner, their excessive muscle tension seemed to act as a resistance which had to be overcome by voluntary neuromuscular effort before it could become effective. With maintenance of this reaction pattern, somatic symptoms eventually resulted. Conceivably, the finely coordinated neuromuscular mechanism outlined above is disrupted under these circumstances, with eventual impairment of muscular efficiency and greater liability of muscles and associated tissues to injury.

The shoulder joint has been described as an especially vulnerable anatomic structure, poorly suited for the demands made upon it.<sup>7</sup> Moreover, the upper extremity is a highly specialized appendage and the major means of carrying into action the aggressive drives of the individual in his constant struggle for survival. These factors might add to the vulnerability of the shoulder.

In the group of patients studied there was no indication that they actually performed any greater amount of work or were more active with their upper extremities than other individuals. The efforts they did make, however, were carried out in the presence of sustained increased muscle tension. Furthermore, none of them suffered injury of any magnitude, yet shoulder symptoms developed. This suggests that in the presence of excessive muscular tension, whether it is secondary to emotional stress or to some other cause, the trivial trauma of daily muscular activity is sufficient to produce injury and resulting symptoms. Under such circumstances, the determining factor in production of symptoms would be the presence of increased muscular tension and the resistance it imposes to voluntary muscle activity. The protracted coexistence of these opposing forces, plus the vulnerability of the shoulder joint, might explain why this structure is so frequently the site of this type of musculoskeletal disability.

As noted, the majority of patients in this study had thoracic pain as their chief complaint. Probably for this reason most of them originally had been considered by their family physician to be suffering from heart trouble or, in the absence of demonstrable cardiac abnormality, from a cardiac neurosis. When it was demonstrated to these patients that the local source of their precordial discomfort was the musculature outside of the thorax they were provided with reassuring and convincing evidence that the heart per se was not responsible for their symptoms and disability. This established a sound basis for pursuing further their underlying emotional and situational problems and the institution of psychotherapy.

In this series psychotherapy was added to the medical, orthopedic and physiotherapeutic measures ordinarily used in the treatment of painful stiff shoulder. Thus far the results have been encouraging. A detailed report dealing with such "combined" therapy will be made when sufficient time has elapsed to permit critical evaluation.

The observations reported in this study would seem to have quite wide application to the problem of painful stiff shoulder in general. Some of the

complexities of diagnosis and therapy in relation to this syndrome may now be more understandable and amenable to resolution. It is felt that the psychosomatic approach should be added to the other fields of specialized knowledge considered necessary for the proper evaluation and treatment of patients having pain and stiffness in the shoulder region.

#### SUMMARY AND CONCLUSIONS

1. Pain and stiffness in the shoulder or adjacent bodily structures were found to occur in 20 per cent of 300 medical patients seen in psychosomatic consultation.

2. The onset and course of shoulder symptoms in these patients were intimately related to certain of their emotional reactions and stressful life situations.

3. Note was made of the importance of these observations to that large percentage of patients having painful stiff shoulder or subacromial bursitis hitherto classified as being of "obscure etiology."

4. Illustrative case summaries were presented.

5. The mechanism whereby emotional stress may contribute to sustained increase in muscle tension and the relevance of this bodily reaction to the pathogenesis of painful stiff shoulder were discussed.

6. It was suggested that the psychosomatic approach be added to the other fields of specialized knowledge considered necessary for the proper evaluation and treatment of patients having pain and stiffness in the shoulder region.

#### BIBLIOGRAPHY

1. Bosworth, B. M.: Calcium deposits in the shoulder and subacromial bursitis, *J. A. M. A.* **116**: 2477-2482 (May 31) 1941.
2. Carnett, J. B., and Case, E. A.: A clinical and pathological discussion of so-called subacromial bursitis, *S. Clin. North America* **9**: 1107-1126 (Oct.) 1929.
3. Codman, E. A.: The shoulder; rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa, 1934, Thomas Todd Co., Boston, Mass.
4. Davis, F. H., and Malmo, R. B.: Electromyographic recording during interview, *Am. J. Psychiat.* **107**: 908-916 (June) 1951.
5. Dynes, J. B.: Subacromial bursitis associated with diseases of the nervous system, *Lahey Clin. Bull.* **3**: 124-127 (April) 1943.
6. Fischer, K. A., and Leatherman, K. D.: The nature of and treatment of tendinitis of musculotendinous cuff of the shoulder and subacromial bursitis, *South. Surgeon* **16**: 132-143 (Feb.) 1950.
7. Gilcrest, E. L.: In discussion of reference 16.
8. Guido, F. R.: Acute calcified subacromial or subdeltoid bursitis, *California and West. Med.* **60**: 69-72 (Feb.) 1944.
9. Haggert, G. E., and Carr, C. R.: Chronic adhesive subacromial bursitis, *New England J. Med.* **229**: 987-996 (Dec. 30) 1943.
10. Holmes, T. H., and Wolff, H. G.: Life situations, emotions and backache, in *Life stress and bodily disease*, 1950, The Williams and Wilkins Co., Baltimore.
11. Houssay, B. A.: *Human physiology*, 1951, McGraw-Hill Book Co., Inc., New York.
12. Jacobson, E.: The physiological conception and treatment of certain common "psycho-neuroses," *Am. J. Psychiat.* **93**: 219-226 (Sept.) 1941.

13. Malmö, R. B., Shagass, C., and Davis, F. H.: Symptom specificity and bodily reactions during psychiatric interview, *Psychosom. Med.* **12**: 362-376 (Nov.-Dec.) 1950.
14. Menninger, W. C.: Psychosomatic medicine: somatization reactions, *Psychosom. Med.* **9**: 92-97 (March-April) 1947.
15. Meyer, A. W.: Further observations upon use-destruction in joints, *J. Bone and Joint Surg.* **4**: 491-511 (July) 1922.
16. Meyerding, H. W., and Ivins, J. C.: Causation and treatment of painful stiff shoulder. Subdeltoid bursitis, periarthritis, tendinitis, and adhesive capsulitis, *Arch. Surg.* **56**: 693-708 (June) 1948.
17. Musser, M. J.: Early diagnosis of emotionally conditioned illness, *J. A. M. A.* **147**: 1030-1032 (Nov. 10) 1951.
18. Paul, L.: Psychosomatic aspects of low back pain, *Psychosom. Med.* **12**: 116-124 (March-April) 1950.
19. Rogers, M. H.: Treatment of subdeltoid bursitis, *Am. J. Surg.* **43**: 292-297 (Feb.) 1939.
20. Rome, H. P.: Neuromuscular and joint diseases and the psychosomatic approach, *M. Clin. North America* **33**: 1061-1069 (July) 1949.
21. Stetson, R. H., and Bouman, H. D.: The co-ordination of simple skilled movements, *Arch. néerl. de physiol.* **20**: 179-254, 1935.
22. Solomon, A. P.: Low back pain: the psychosomatic viewpoint, *Indust. Med.* **18**: 6-12 (Jan.) 1949.
23. Young, H. H.: Symposium on pain in the shoulder and arm; introduction, *M. Clin. North America* **26**: 799-800 (Aug.) 1946.

## CASE REPORTS

### ACUTE DIVERTICULITIS OF THE CECUM\*

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ACUTE diverticulitis of the cecum is a relatively rare condition in the experience of the average general surgeon. Ochsner and Barger<sup>1</sup> reviewed 151 cases of uncomplicated diverticulosis of the colon and found that in about 2 per cent of the cases the diverticula occurred in the right half of the colon. The incidence of acute inflammation in the cecal diverticula is certainly extremely low. The average age incidence of such cases is approximately 39 years,<sup>2</sup> occurring about equally in both sexes. In one third of all cases, a history of previous attacks of right lower quadrant pain can be elicited.

Since the clinical picture is quite acute and indistinguishable from acute appendicitis, almost all cases go to surgery with a preoperative diagnosis of acute appendicitis. This was the clinical impression preoperatively in the case to be presented.

#### CASE REPORT

A 37 year old female was seen on August 21, 1950, because of severe right lower quadrant pain with anorexia and no nausea or vomiting. She admitted to having had pain in the upper abdomen for the previous two days, constant and moderately severe and aggravated by walking.

*Past history* (revealed postoperatively) indicated similar recurring episodes of milder degree.

*Physical examination* revealed an acutely ill white female doubled up in pain. Temperature was 100.6° F., rectally; pulse, 90. There was muscle spasm in the right lower quadrant, with deep tenderness and rebound pain. There was tenderness on rectal examination. White blood cells, 13,400; polymorphonuclears, 82; lymphocytes, 11; monocytes, 7; urinalysis, normal. The preoperative diagnosis was acute appendicitis.

At operation the appendix appeared normal; however, an appendectomy was performed. Two centimeters from the base of the appendix a mass measuring about 6 by 3 by 2 cm. was palpable in the cecum. It was debated whether to biopsy the lesion because of the possibility of its being an inflammatory granulomatous mass but this was not done. The pelvic organs were negative except for adhesions from the right Fallopian tube to the cecum medial to the base of the appendix where the mass was felt. The patient made an uneventful recovery.

Postoperatively a barium enema was unsuccessfully attempted. On October 4 a repeat barium enema revealed diverticula throughout the transverse and ascending colon and at the tip of the cecum (figure 1).

The patient remained asymptomatic and was placed on a low residue diet.

When last seen, 16 months postoperatively, there were no complaints.

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FIG. 1.

## COMMENT

Local sequelae following acute diverticulitis of the cecum are: (1) perforation with localized or generalized peritonitis; (2) gangrene of the diverticulum; (3) abscess formation, usually involving the right portion of the cecum, peritoneum in the right lower quadrant and the omentum; (4) multiple adhesions in the area of the diverticulum; (5) enterointestinal fistula, or enterovesical fistula, or enterocolic fistula, or others; (6) retrocecal abscess; (7) extraperitoneal abscess.

There is a diversity of opinion as to the proper treatment for acute cecal diverticulitis. This should be governed by the findings at the time of operation.

A hemicolectomy may be performed in any one of the aforementioned instances. Likewise, any suspicious looking granulomatous lesions would indicate a more drastic surgical approach, with section of the colon. In a simple case such as the one herein presented, however, where a simple inflammation of the diverticulum is found, there is no need for surgical intervention. Medical management with proper diet would be the treatment of choice.

#### BIBLIOGRAPHY

1. Ochsner, H. C., and Bagen, J. A.: Diverticulosis of the large intestine: an evaluation of historical and personal observations, *Ann. Int. Med.* 9: 282, 1935.
2. Anderson, L.: Acute diverticulitis of the cecum, *Surgery* 22: 479, 1947.
3. Henry, F. C.: Acute diverticulitis of the cecum, *Ann. Surg.* 129: 109, 1949.

### PRIMARY HYPERPARATHYROIDISM REQUIRING PROLONGED POSTOPERATIVE THERAPY \*

By IRWIN S. ESKWITH, M.D., *Bridgeport, Connecticut*

PRIMARY hyperparathyroidism is an easily diagnosed condition. Because of its comparative rarity, however, the possibility of its existence is frequently overlooked. The case to be described had her first episode of renal lithiasis at the age of 30, and the diagnosis of parathyroid adenoma was not made until the age of 62. This duration of symptoms is longer than in any case I have been able to find in the literature. Postoperatively, decalcification and hypocalcemia were so severe that intensive parenteral therapy was necessary. This, too, was carried out for a longer period of time than in any case I have found in the literature.

It is primarily because of the postoperative therapeutic problem that this case is presented. In addition, the long duration and the cardiac findings were thought to be of interest.

#### CASE REPORT

A 62 year old female was first seen in my office on April 11, 1950. Her chief complaint at that time was palpitation, more or less constant, of 14 months' duration. This was worse after each meal and upon retiring, but she had continual heart consciousness. In 1926, at the age of 30, she had been admitted to St. Vincent's Hospital, Bridgeport, Connecticut, where a left ureteral calculus was removed. In 1938 she was admitted to the same hospital for an episode of bronchial pneumonia, and in 1940 the left kidney was removed because of infection and renal stones. In June, 1947, a painful tumor about the size of an egg appeared on the upper medial aspect of the left tibia and was removed; the pathologic diagnosis was that of a giant cell sarcoma. At this time she first developed mild palpitation. In 1949 she had another admission because of anemia, which was treated with blood transfusions. In January, 1950, she had still another hospital admission because of weakness, fatigue, numbness and tingling of the hands and feet. Sinus tachycardia and frequent extrasystoles were noted at that time. The patient received two transfusions and was discharged. When seen in my office, she stated that for two years she had had severe pains in the legs,

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back and chest. Pain was worse at night. The patient was certain that the pain was not articular but rather in shafts of the bones. She stated that she drank tremendous amounts of water. She also had polyuria. During the night she had marked heat intolerance and perspired profusely. In one year she had lost eight pounds. Although she had sought medical help for this pain, she had gained no relief in spite of injections of gold, vitamin B<sub>12</sub> and other medication. Over a two year period the patient had noticed a gradual change in the shape of her fingers, with widening of the distal phalanges. Past history revealed, in addition to the hospital admissions mentioned, a cholecystectomy 20 years before and a hysterectomy for fibromyoma. Family history was noncontributory.

Physical examination revealed a small, pale, apprehensive female in no acute distress. The pulse was 100; blood pressure, 150/100 mm. of Hg; weight, 127 pounds. There was slight prognathism present, and there was a peculiar type of enlargement of the antero-posterior diameter of the chest, with forward bowing of the sternum. The lung fields were clear. The cardiac apex was visible at the sixth interspace at the anterior axillary line. A marked systolic thrill was present over the mitral area and a loud systolic murmur at the apex and aorta. The abdomen was essentially negative upon examination. There was tenderness on pressure of the bones of the extremities. Fluoroscopy revealed a moderately enlarged heart and slight pulmonary fibrosis. The aorta was diffusely dilated. It was felt that the diagnosis must lie between multiple myeloma and hyperparathyroidism. The patient was re-admitted to St. Vincent's Hospital, where a blood calcium was 12.0 mg.; phosphorus, 6.7 mg., and alkaline phosphatase, 22 units. Because of the high phosphorus the laboratory work was repeated, showing calcium of 13.9 mg. and 14.0 mg.; phosphorus, 2.5 and 2.45 mg. A urine Sulkowitch test showed a 3 plus reaction. X-ray films (figure 2) revealed marked osteoporosis of all the bones, with pseudocyst formation. On April 21, 1950, a bone marrow smear was performed. The needle penetrated the sternum as if it were cardboard. Examination of the smear revealed normal marrow constituents. The electrocardiogram revealed sinus tachycardia and a QT interval of 0.36 second. Because of the history and laboratory findings, which were all rather typical, it was felt that this patient had a parathyroid adenoma. On April 22, 1950, an operation was performed by Dr. William Curley, Jr. The lower left parathyroid gland consisted of a hard round tumor, almost the size of a walnut, which on biopsy was found to be a benign adenoma of the parathyroid gland. The tumor weighed 6 gm. and measured 3 by 1.5 cm. At operation, three other normal appearing parathyroid glands were identified. The first postoperative day was accompanied by mild oliguria, and during the evening the patient developed paresthesias of the fingers and mild body twinges, which were relieved by one injection of 10 c.c. of 10 per cent calcium gluconate. On April 25, 1950, three days after the operation, it was noticed that the thrill, murmur and cardiac hyperactivity had disappeared. The cardiac signs were now essentially normal and the QT interval had increased to 0.44 second. On April 24, 1950, blood calcium was 7.4 mg.; phosphorus, 2.4, and phosphatase, 44 B.U. Non-protein nitrogen was 44 mg. per cent. The patient continued to have mild tetany, and on May 1 the serum calcium had fallen to 6.4 mg. The patient left the hospital against advice on May 1, 1950. The next night, at home, laryngeal stridor and severe twitching of the body appeared. Calcium gluconate was administered and the patient was re-admitted to the hospital, at which time a negative Sulkowitch and a calcium of 5.6 were reported. Phosphorus had increased to 2.7 mg. The patient was given 8 gm. of calcium gluconate by mouth and 2 gm. intramuscularly daily. She was discharged slightly improved on May 13, 1950. She continued to have signs of hypocalcemia and was re-admitted to St. Vincent's Hospital on May 26, 1950, where on admission her calcium was 5.7 mg. and her phosphorus, 2.3. It was decided to treat her with intravenous infusions of 100 c.c. of 10 per cent calcium gluconate dissolved

in a liter of 5 per cent dextrose, as mentioned by Albright.<sup>1</sup> She received this daily throughout her stay in the hospital, until June 13, 1950. This resulted in marked amelioration of the symptoms, and the blood calcium rose to 9.6 mg. At home she continued to receive the infusions containing 10 gm. of calcium gluconate two to three times weekly. In addition, since it was felt that postoperative hypoparathyroidism might be present, AT-10 was administered orally. Regardless of the dose used, the patient complained bitterly of bone and joint pain similar to that before the operation. The drug was discontinued. In addition, she received 10 gm. of calcium gluconate orally, and stilbestrol. An interesting finding was the fact that, in spite of the low blood calcium, a Sulkowitch test giving a 2 plus reaction continued. Personal correspondence with Fuller Albright, M.D.,<sup>1</sup> elicited his opinion that she had a mild pyelonephritis. Large doses of vitamin D were also given without relief. The in-

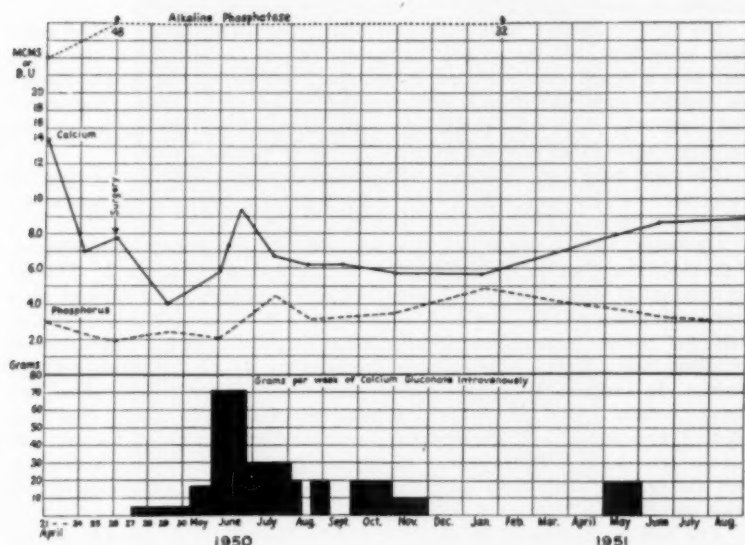


FIG. 1. Graph shows the calcium and phosphorus levels and parenteral therapy required postoperatively. In addition, 8 to 10 gm. of calcium gluconate orally were given daily.

fusions were continued from June 15 to November 8, as the accompanying chart shows (figure 1). At the end of this time the patient felt better and had fewer symptoms, although the calcium continued to vary between 5.4 and 7.0 mg. per cent. She was able gradually to increase her activity, and paresthesias appeared only intermittently. During the month of May, 1951, the paresthesias became quite severe, and she received infusions three times weekly for that month. Since then the patient has been slowly improving. The last blood calcium determinations were 8.3 and 8.8 mg. per cent. The phosphorus was 3.8 mg. The hemoglobin is now 9.5 gm. The patient's weight has increased to 150 pounds. She still has occasional paresthesias, but they are diminishing. She still has pain in the left tibia. Her symptoms should diminish, since it would appear from the x-ray film that the greatest part of the recalcification has been accomplished.

## DISCUSSION

There are at least three rather interesting features of this case, namely, the long duration of the illness, the prominence of the cardiac signs and symptoms, and the prolonged therapy necessary to elevate the blood calcium.

Since renal calculi are frequently the initial sign of this disease, the onset of the patient's illness may be set at 1926, when she was 30 years old. Thus, 32 more years elapsed before the diagnosis was made, during which period she received treatment for anemia, bone cysts and further renal complications. In Black's<sup>2</sup> series, the mean duration of the disease with bone changes and calculi was slightly over 10 years. Burke<sup>3</sup> mentions a patient whose symptoms lasted for 10 years, and Lace and Greene's<sup>4</sup> longest case had had complaints for 13 years. In another series<sup>5</sup> the duration ranged from 11 to 16 years.

The cardiac findings were extremely interesting. The patient's chief complaint when first seen was severe palpitation. Upon examination of the heart, there were a strong apical thrill and a loud apical murmur. It seemed as though the hypercalcemia had caused increased cardiac activity. These disappeared postoperatively. When the patient received her intravenous calcium too quickly she would again experience the same distressing palpitation.

The most engrossing feature of this case was the intensive therapy required postoperatively to restore calcification of the bones and maintain the serum calcium at a satisfactory level.

Obviously, because of the long duration of the illness, marked decalcification of the skeletal system had occurred. This is clearly shown in figure 2. Following removal of the adenoma, the bones consumed calcium as a man lost on a desert consumes water when it is offered to him. Because of what Fuller Albright<sup>6</sup> terms "hungry bones," large amounts of calcium were administered for a long time. Figure 1 shows the intravenous calcium gluconate administered weekly. In addition, the patient took orally between 8 and 10 gm. of calcium gluconate daily. The end results were quite satisfactory, as can be seen from figure 3, and the calcium determinations on the chart. At times, however, we felt we were dealing with secondary hypoparathyroidism with tetany, and it was only the certainty that three normal glands had been found at operation that made me continue therapy.

The Sulkowitch reagent proved of little aid as an indication of serum calcium levels. As has been mentioned, this may have been due to a low grade renal infection. This should be borne in mind when this test is used and the kidney status evaluated, should the results prove contradictory to the clinical picture.

The use of A.T.-10 rapidly reproduced her symptoms of bone pain, another indication of her severe decalcification existing here and a hint that hypofunction of the glands was not the cause of tetany.

## CONCLUSIONS

A case has been presented of primary hyperparathyroidism with marked skeletal decalcification requiring prolonged therapy. It illustrates that osteitis fibrosa cystica, when the cause is removed, may result in such rapid and prolonged withdrawal of calcium from the serum that an adequate serum level of this substance is almost impossible to maintain. Thus tetany and paresthesias identical with those of true hypoparathyroidism may occur. Before concluding that

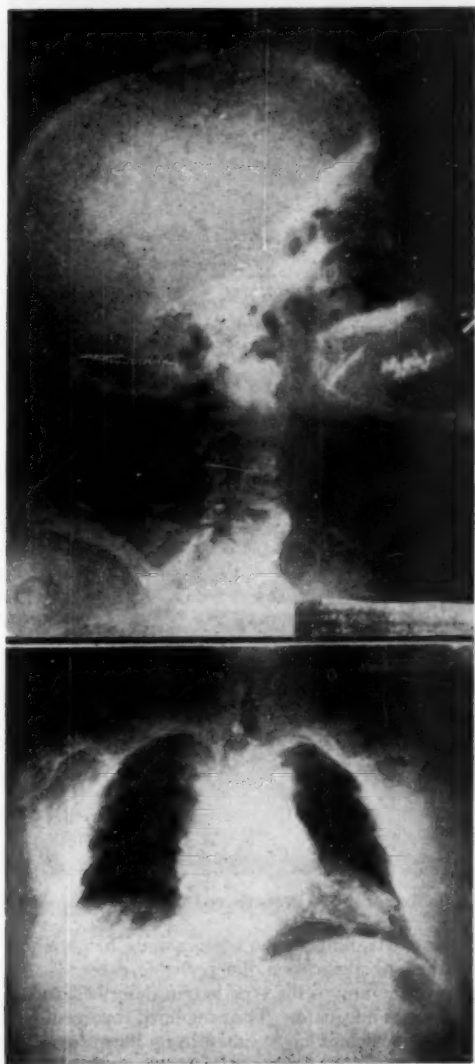


FIG. 2. Films taken on admission to the hospital. Note the mottling of the skull and the loss of the inner and outer tables. There are marked osteoporosis and resorption of the clavicle and ribs.

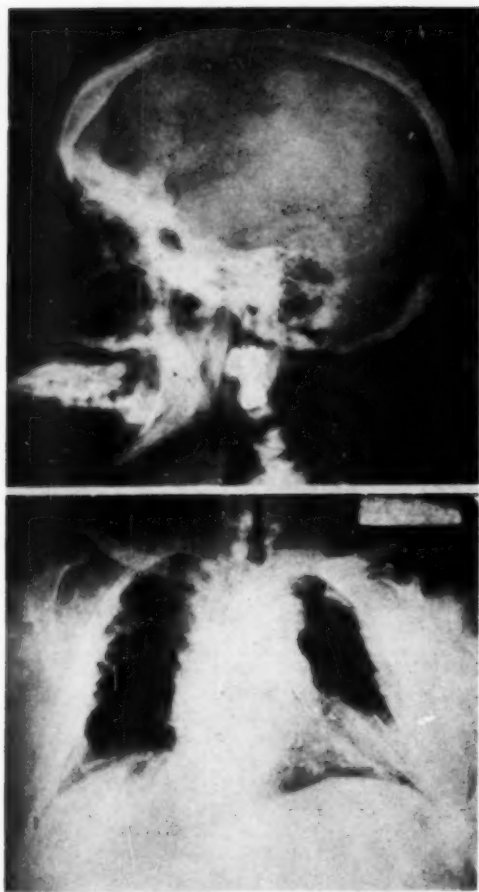


Fig. 3. Films taken in August, 1952. Note the recalcification of the skull, clavicles and ribs.

this latter syndrome exists, films of the bones should be obtained. If these continue to show marked decalcification the probable cause of the tetany is bone hunger, and intensive therapy of the type herein described should be carried out until recalcification seems adequate. The prolonged treatment with large amounts of oral and intravenous calcium has resulted in no harm to the patient.

#### BIBLIOGRAPHY

1. Albright, F.: Personal correspondence, Sept. 18, 1950, to December 27, 1950.
2. Black, M. B.: Surgical aspects of hyperparathyroidism, *Surg., Gynec. and Obst.* 87: 172, 1948.

3. Burke, L. B.: Hyperparathyroidism: an analysis of ten cases with special references to early diagnosis, *Am. J. Surg.* **76**: 404, 1948.
4. Lacey, R., and Greene, J. A.: Hyperparathyroidism: a report and an analysis of thirteen cases occurring in the Middle Western States, *J. Clin. Endocrinol.* **3**: 408, 1943.
5. Alexander, H. B., Kirk, E. J., Pemberton, J., and Broders, A. C.: Functional parathyroid tumors and hyperparathyroidism, *Am. J. Surg.* **65**: 157, 1944.
6. Albright, F.: Parathyroid glands and metabolic bone disease, 1948, Williams and Wilkins Co., Baltimore, Maryland.

### **POLYARTERITIS NODOSA CAUSING DEAFNESS IN AN ADULT: REPORT OF A CASE WITH SPECIAL REFERENCE TO CONCEPTS ABOUT THE DISEASE \***

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#### **HISTORICAL AND ETIOLOGIC CONCEPTS**

As early as 1755, Matani<sup>1</sup> described nodules upon small arteries. Similar lesions were again described independently by von Rokitsansky<sup>2</sup> in 1852, but the pathologic findings were not definitely related to the clinical picture until 1866, when Kussmaul and Maier,<sup>3</sup> unaware of the work of Matani and von Rokitsansky, described a protean clinical syndrome associated with nodular arterial lesions and coined the name "periarteritis nodosa." Their case was a 27 year old white man who gave a history of sudden onset of an illness characterized by muscular weakness and tenderness, paresthesias, diaphoresis, mild fever and progressive emaciation. During the course of observation the patient developed, in addition, low back pain, intermittent colicky abdominal pains, subcutaneous "pea-sized" nodules and a progressive widespread, nonsystematic paralysis marked by exacerbations and remissions. The remissions were short and the over-all picture rapidly became worse. Kussmaul and Maier remarked that it was easier to give a prognosis than a diagnosis. They could not fit all of the findings into any known pathologic process, and concluded that they were dealing with either a little known or an unknown disease. The patient died about four months after the onset. At necropsy, small white nodules the size of "poppy seeds" or "hemp seeds" were seen in the striated muscles, suggesting parasitic encystment to the gross examiners. However, Ecker and Manz, who studied these focal lesions microscopically, described them as "aneurysmal thickenings" of small arteries. The preliminary impression that an unusual type of filariae was seen in sections prompted Kussmaul and Maier to report small arterial aneurysms due to worms. It was later proved that these were not true filariae, and in a second article these same investigators reported that they could not shed much light on the

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important question of the etiology. The lesions were noted to occur only in the small arteries, and it was their belief that an inflammatory process began in the arterial sheath and spread outward. Specimens were sent to Virchow to see if this were really a new disease. He reported that he had seen similar but less extensive lesions in syphilis, and for years it was the impression of many that periarthritis nodosa was an unusual form of syphilis.

In 1903, Ferrari<sup>4</sup> recognized that all coats of the arteries are involved, and suggested that the name "polyarteritis nodosa" was more nearly true than periarthritis nodosa.

Since that time about 500 cases have been reported, though undoubtedly there have been many more, and the disease still exists as a syndrome characterized by a variability of findings suggesting many afflictions in the same person, which are readily accountable by knowledge of the fundamental process. As the name implies, the disease is an arteritis that can affect all coats of medium sized and small arteries. Though it is possible, veins and larger arteries<sup>5</sup> are rarely involved. One vessel in one organ,<sup>6</sup> or several in two organ systems, or many in practically every organ system of the body may be affected. The clinical picture and possible diagnoses vary accordingly. The lesions may remain localized<sup>6</sup> for a long while and then either spread or disappear.<sup>7</sup> They are often small and easily missed even at necropsy,<sup>7</sup> and attempts to correlate the clinical picture and the pathologic findings are incomplete unless extensive serial sections are done.

The etiology of polyarteritis nodosa remains obscure. Arkin,<sup>8</sup> in his classic review of the pathology in 1930, discussed previous etiologic concepts. He emphasized the fact that other workers had found similar lesions in syphilis, rheumatic fever and in various infectious diseases, and considered periarthritis nodosa a form of postinfectious mesarteritis. He also indicated that a like disease occurs in calves, swine, dogs and deer, sometimes in epidemic form, and that he felt a virus was responsible. As yet, however, no virus has been isolated, nor have spirochetes, bacteria, rickettsiae or parasites been shown in the lesions,<sup>10</sup> and much work has been done to demonstrate that they are due to the reaction of a special host<sup>11</sup> to any or all of the following: bacterial toxins,<sup>10</sup> serums, sulfonamides,<sup>9</sup> thiouracil,<sup>12</sup> allergens of all sorts, or anything that will bring about the alarm reaction,<sup>13</sup> including cold, colchicine, morphine, emotion and trauma. Gruber<sup>9</sup> in 1923 produced the same type of lesions in sensitized animals, and was the first to suggest that hypersensitivity might be the cause. Rich and Gregory<sup>9</sup> in 1943 produced like lesions in sensitized as well as nonsensitized laboratory animals with serums and sulfonamides. Further substantiating hypersensitivity as the cause of periarthritis nodosa, they found several cases in human beings who had received sulfonamides or serums.

Klinge<sup>14</sup> in 1933 was the first to focus attention upon the fibrinoid connective tissue damage in periarthritis nodosa, dermatomyositis, malignant nephrosclerosis, thromboangiitis obliterans, certain nephritides, subacute bacterial endocarditis, rheumatic fever and rheumatoid arthritis; others added scleroderma and lupus erythematosus to the list. Klinge observed connective tissue damage in rabbits made hypersensitive to foreign protein, and concluded that hypersensitivity was the cause. Banks<sup>15</sup> reports that the vascular lesions in many of these diseases are similar, and that some cases begin as one and may terminate as another. He wonders if they all may not have the same "denominator."

Klemperer<sup>16, 17</sup> more fully developed the concept of collagen diseases in 1950, and challenged the idea that hypersensitivity is the basic cause. He illustrates that numerous similar fibrinoid collagen alterations can be provoked by different injuries, and well demonstrates that it is unwarranted to infer that all these diseases are closely related pathogenetically. Despite the fact that sulfonamides have been in great use since 1931, Griffith and Vural,<sup>18</sup> who found 16 cases out of 19,242 autopsies at the Los Angeles County Hospital from 1939 through 1949, could not find an increase in polyarteritis nodosa due to sulfonamides, nor a close etiologic relationship between allergy and the disease.

#### PATHOLOGY

Arkin<sup>5</sup> separates the panarteritis into four stages. He believes the process begins in the media and is characterized by hyaline degeneration and separation by edema. Then inflammatory cells, especially polymorphonuclear neutrophils, eosinophils, lymphocytes, plasma cells, histiocytes and occasionally giant cells, invade the necrotic area. Invasion of the adventitia and interna is usual and can involve the entire circumference of a vessel or just part of it. Serial sections often show the lesions to be elliptical, with the greatest diameter parallel to the long axis of the vessel. They are often less than 1 mm. in diameter, but can be much larger. Following this inflammatory stage, granulation tissue rich in fibroblasts and capillaries replaces the lesion in the vessel wall, and is apt to spread into the surrounding tissue. Giant cells are sometimes seen not only in the vessel wall but also in the surrounding granulation tissue.<sup>19</sup> Thromboses or aneurysms often occur. The latter may rupture<sup>8</sup> and can cause fatal hemorrhage. Occlusion of the blood supply to a vital organ by thrombosis also can cause rapid death. Pain is usually associated with the lesions, probably due to the pulsating arterial pressure, with resultant stretching and relaxing of the irritated necrotic areas.<sup>20</sup> Finally, scar tissue replaces the injured vessel wall and either completely occludes the lumen or greatly narrows it. If the process extends beyond the outer media and adventitia, nodular thickenings occur and produce the findings whereby the disease was first named. Actually, these nodules occur in 23 per cent of patients and only rarely can any be felt under the skin.<sup>21</sup>

Once the lesions begin they can progress to the healing stage rapidly,<sup>21, 22</sup> but new ones usually occur and it is not uncommon to see all stages in one individual. In some cases, however, the pathologic findings can be very meager.<sup>7</sup> Apparently at times the inciting agent disappears or resistance to it develops, because there are some spontaneous cures, about 5 to 10 per cent, according to Rose, Littmann and Houghton,<sup>23</sup> and 50 per cent according to Grant.<sup>7</sup> One patient with hypertension and urinary findings has been reported living and well six years after treatment by splanchicectomy.<sup>19</sup> There is some evidence that cortisone tends to heal the lesions.<sup>24</sup>

Men are affected at least three times as often as women.<sup>7, 19</sup> It can occur at any age; the youngest case reported was 10 days old, the eldest 77 years.<sup>18</sup> The highest frequency of occurrence is in males from 20 through 40 years of age. Those cases without renal involvement seem to live longer than those with it. When death occurs, it is usually within two years of the onset of symptoms.<sup>25</sup> Cases have been reported from many places in the world. Some authors have felt that those patients with skin lesions are apt to have a milder course,<sup>26</sup> with a

better chance for spontaneous cure. However, this was not the experience in our patient, whose course was characterized not only by severe, recurrent skin lesions but also by the unusual finding of complete bilateral deafness. His course lasted four years and seven months and terminated by cerebral hemorrhage.

#### CASE REPORT

The patient was a short, obese, 46 year old auto mechanic from Nevada. He had had gonorrhea in 1924, which was treated by irrigations, and an operation upon a urethral stricture in 1947. There was no personal or family history of asthma, hay fever or hives. He had had no serious illness.

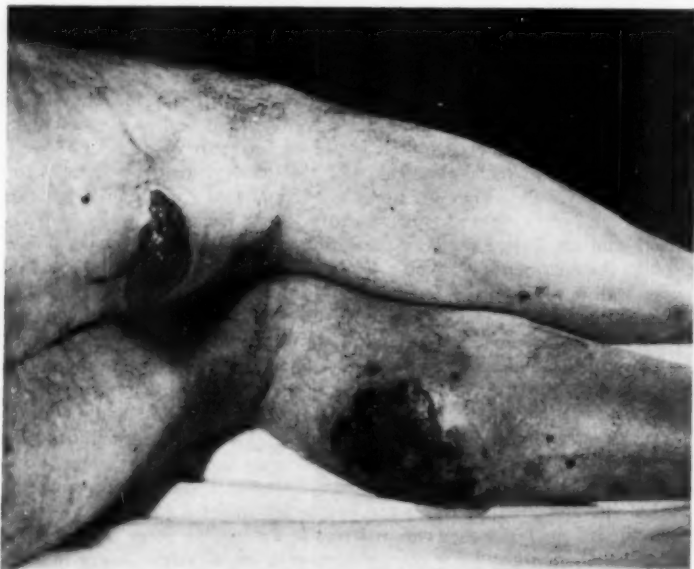


FIG. 1. Demonstration of typical large ulcerations of skin during the acute phase. Note the smaller scattered satellite purpuric lesions.

The onset in October, 1946, was acute and characterized by pain deep in the muscles near the bone in both calves and back of both thighs, especially the right. There was mild tenderness in the right calf but not elsewhere. At the same time about a dozen tender purpuric lesions, approximately 4 mm. in diameter, appeared on all aspects of both legs.

He was treated by a physician with penicillin intramuscularly. After a few injections, according to the patient, a weeping eruption appeared which was followed by desquamation of the skin from the genitalia and buttocks. The purpuric lesions progressed in size and many developed necrotic centers with ulceration (figure 1). Penicillin was discontinued and sulfonamides were used, but an urticarial reaction ensued. Sulfonamides were then discontinued. The lesions would eventually heal, leaving atrophic scars of various sizes. However, new crops of purpuric and ulcera-

tive areas continued to appear, chiefly on the lower extremities, genitalia and buttocks (figure 2). After a period of approximately eight months the eruption cleared and in association with this clearance the pain in the calves ceased.

In July, 1947, the patient was hospitalized in Nevada because of severe pain in his back which developed when he suddenly straightened up after stooping over. He had no leg pain at this time or evidence of recurrence of his cutaneous lesions. Be-



FIG. 2. Cutaneous lesions from the left popliteal space. The lower ulcerated area was typical of a new active lesion with a raised, erythematous, sharply demarcated border and thick, adherent eschar. The upper lesion shows the terminal phase of the process, with a residual large, atrophic scar.

cause of the presumptive diagnosis of severe psychoneurosis, he was given insulin shock therapy on three occasions.

On December 30, 1947, he entered Birmingham Veterans Administration Hospital for the first time, complaining of the reappearance of the "sores" on his legs. No other significant abnormalities were found after careful physical examination. His blood pressure, pulse and temperature were normal. Numerous discrete, small, hemorrhagic, hyperpigmented lesions studded both his legs. Some of the larger ones were ulcerated, with sharply demarcated borders and central areas of grayish, adherent eschars. There was a similar ulcer in the mouth near the right anterior pillar.

Scattered on the calves, thighs and buttocks were various sized, round to oval healed atrophic scars.

The patient was referred to the diabetic service because two glucose tolerance tests showed a three hour blood sugar over 200 mg. per cent. He was placed on a reducing diet. After the loss of a few pounds, a new shower of purpuric lesions appeared not only on his lower extremities but also on the upper extremities and the external ears. Tissue specimens from the lesions were cultured and examined microscopically. The cultures were noncontributory. Histologic examination showed non-specific vascular changes and granulation tissue consistent with chronic dermatitis.

On two occasions he was presented as a diagnostic problem to the Los Angeles Dermatologic Society. No definite diagnosis was made there but it was suggested that, in view of the nonspecific findings, he might have a nodular vasculitis of non-tuberculous origin.

Large doses of vitamin D were given and in two more months his skin was once again healed, with extensive scar formation. He was discharged on June 19, 1948.

He enjoyed good health for one month. On July 18, he awoke with a rushing noise in his ears. The left ear felt plugged. An hour later he became dizzy and noted the room going clockwise; he could not walk. The dizziness subsided in a few hours. Two days later he came to the hospital because of severe tenderness in the left calf and left leg, with stiffness and soreness of the joints. His blood pressure was 130/80 mm. of Hg; pulse, 84 and regular; temperature, 98.6° F. A biopsy specimen of muscle tissue from the left calf was normal. Audiometer and voice tests revealed complete deafness of the left ear. The diagnosis was thrombosis of the left internal auditory artery.

About August 26 a new crop of erythematous and purpuric lesions varying in size from 0.2 to 1 cm. in diameter appeared on the extremities, buttocks and the upper part of the back, as well as on the external ears and nasal mucous membranes. He had several bouts of epistaxis, was treated with nasal packs, and developed a left otitis media. He improved slowly.

On January 10, 1949, his right eyelid suddenly drooped, his face felt stiff, and his lips tingled as if they had been injected with Novocain. When he stepped out into the cold air (20°F.), the entire left side of his body felt hot, whereas the right side became cold. He noted a mild disturbance in equilibrium. Neurologic examination revealed a right pupil of 4 mm. and a left pupil of 5 mm. Both reacted to light and accommodation. The left ear was totally deaf, the right had mild impairment of hearing to whispered voice. The right knee jerk was greater than the left and there was a right Babinski reflex. There was a definite, though mild, left hemihypalgesia and hypothermalgia and slight truncal ataxia. Clinically these findings were thought to suggest multiple areas of necrosis due to unspecified vascular lesions, occlusion of the left auditory artery, and some impairment of circulation of the right superior cerebellar artery. Later there was a subsidence of the patient's neurologic symptoms, and the skin lesions healed by March, 1949. Vitamin D in massive doses had no apparent effect on the skin. Eight grams of aureomycin, given in the early part of February, seemed to help the healing process. He was discharged on April 4, 1949.

He returned on September 23, 1949, because six days previously he had begun to have black, tarry bowel movements and had gradually become weak and dizzy. He had no remarkable abdominal pain. His blood pressure was 130/80 mm. of Hg; temperature, 98.6°F. Other than an obvious anemia due to hemorrhage (red blood cells, 2,520,000; hemoglobin, 7.5 gm.; hematocrit, 25 mm.; 4 plus occult blood in the feces), the laboratory findings were not remarkable. They included a complete blood count, urinalysis, albumin-globulin ratio, electrocardiogram, gastroscopy, sigmoidoscopy, upper gastrointestinal x-ray series and barium enema. He responded well to five blood transfusions and his stools soon became free of occult blood. There was no

history of abdominal pain and no abdominal tenderness. There were indurated, ulcerating lesions on his hands, forearms and legs.

After correction of the anemia, his blood pressure was found to be elevated for the first time. It was checked four times a day for 10 days and averaged 140/100 mm. of Hg. By October 26 the skin lesions once again had healed. He was asymptomatic and was discharged November 9, 1949.

He returned again on December 23, 1949, because of the sudden loss of hearing of the right ear associated with dizziness. His equilibrium returned in a few days, but examination by speaking tests and audiometric studies revealed total deafness in both ears. His blood pressure was now 170/110 mm. of Hg; pulse, 84 and regular;

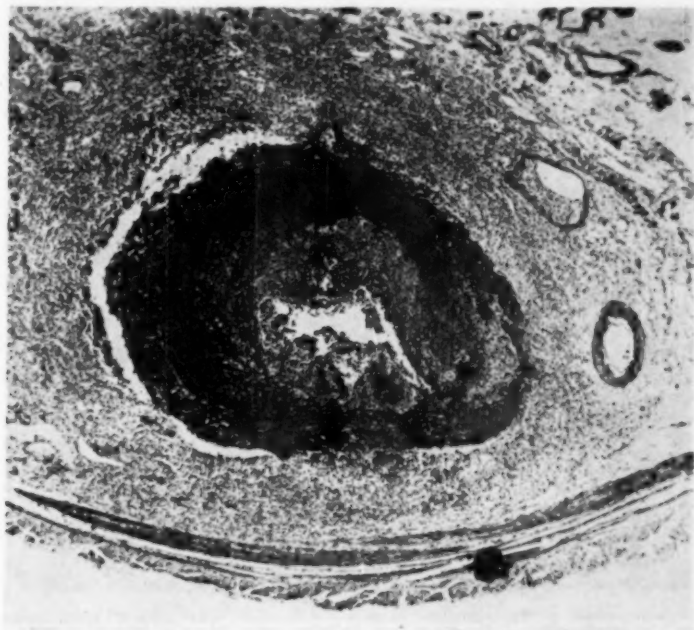


FIG. 3. Medium sized artery, jejunum. H & E  $\times 20$ . Note the marked necrosis of wall of medium sized artery with early thrombus formation.

temperature, 98° F. He was still obese and did not appear acutely ill. Complete blood count, urinalysis, albumin-globulin ratio, and sputum, stool and urine cultures for *Mycobacterium tuberculosis* were noncontributory.

On January 18, 1950, he awoke from a sound sleep at 3:20 a.m. because of the sudden onset of pain in the left lower quadrant, accompanied by nausea and a sensation of warmth. There were no significant gastrointestinal or urinary findings. The abdominal pain became intermittent until his death.

The eruption recurred on the flexor surface of his right arm on February 1. By February 25 a great many new purpuric lesions had appeared on his legs and were very painful. He now looked severely ill. His temperature remained normal. The

sedimentation rate was 49 mm.; white blood cell count, 7,800, including 66 per cent polymorphonuclear leukocytes and 4 per cent eosinophils. Urinalysis was normal. He again gradually improved and his skin completely healed by June, 1950.

Paresthesias of an ulnar nerve distribution were noted in both hands in July, 1950.

One definite asthmatic attack occurred on September 26, 1950. It lasted a short while and required no specific medication. No other similar episodes were noted. His blood pressure was then 170/105 mm. of Hg. There was no evidence of cardiac failure.

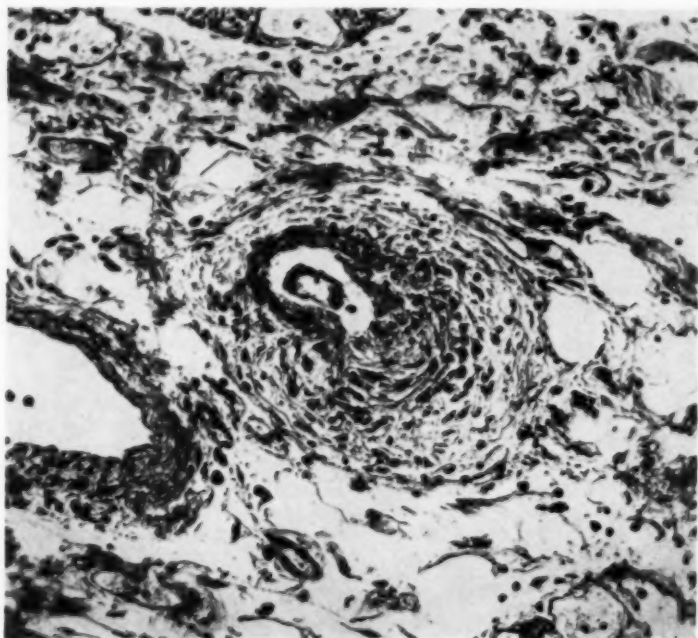


FIG. 4. Small artery, jejunum. H & E  $\times 420$ . Note focal area of hyalinization of media and proliferation of fibroblasts and reticular cells. There is elevation of the proliferative endothelium of intima.

He improved and went home in May, 1951. He returned comatose on June 1, 1951. His blood pressure was 230/90 mm. of Hg, and the spinal fluid was grossly bloody, with a pressure over 600 mm. of water. He died on June 5, 1951.

*Essential Necropsy Findings:* The body was well developed and nourished. Several scars were present on the lower abdomen and legs. The right and left lungs weighed 750 gm. and 650 gm., respectively. The lungs showed several areas of recent bronchopneumonia in the upper lobes and edema and congestion in the lower lobes. There were several scattered old pleural adhesions bilaterally. The heart weighed 350 gm.; the myocardium of the right and left ventricles measured 0.3 and 1.4 cm., respectively. Small hyaline and fatty plaques were present in the intima of the patent coronary arteries and aorta. The liver was moderately enlarged and congested.

There was a moderate increase in connective tissue in the portal areas. The pancreas showed an increase in perilobular fibrosis and moderate thickening and hyalinization of arterioles. The adrenal glands revealed no significant changes. The kidneys were slightly decreased in size and the surfaces finely granular. Microscopically, the arterioles were moderately thickened and hyalinized. The testes showed fairly active spermatogenesis.

The most important lesions were found in the intestines, spleen and skin. Within the mesentery and adventitia of the small intestines there were small, round, grayish-white firm nodules measuring up to 3 mm. in diameter. Surrounding the nodules

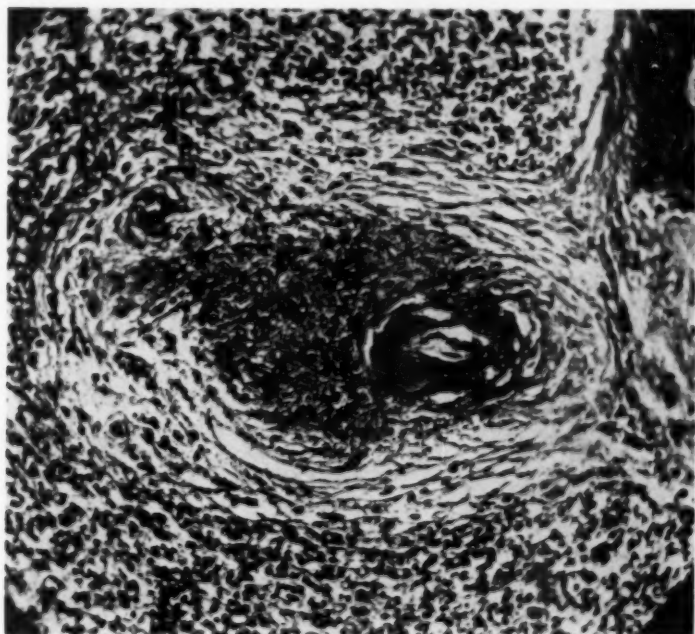


FIG. 5. Small artery, spleen. H & E  $\times 180$ . Note necrosis of wall of artery. Marked perivascular proliferation of fibroblasts and reticular cells. Intima elevated.

there were small hemorrhages. Microscopically, the nodules consisted of areas of necrosis with infiltrations of polymorphonuclear leukocytes and histiocytes. A medium sized artery in one such area showed necrosis of the wall with an early thrombus formation (figure 3). An arteriole in a similar area revealed focal areas of necrosis of the wall, with mural and perivascular collections of fibroblasts and reticular cells (figure 4). Similar lesions of arterioles were found in the spleen (figure 5), which was enlarged and weighed 300 gm. Sections of the skin showed a small subcutaneous artery in which there was marked proliferation of fibroblasts and reticular cells in the subintimal connective tissue, with formation of multinucleated giant cells (figure 6). There were also several scars.

Examination of the brain revealed a recent hemorrhage occupying and destroying almost the entire left cerebrum; the base of the brain and adjacent brain stem showed recent petechial hemorrhages. The site of rupture of the cerebral vessel could not be determined, and microscopic examination of the brain and meninges failed to show changes in the arteries except for moderate sclerosis. Each eighth cranial nerve showed degenerative changes with loss of myelin and fragmentation of the axis

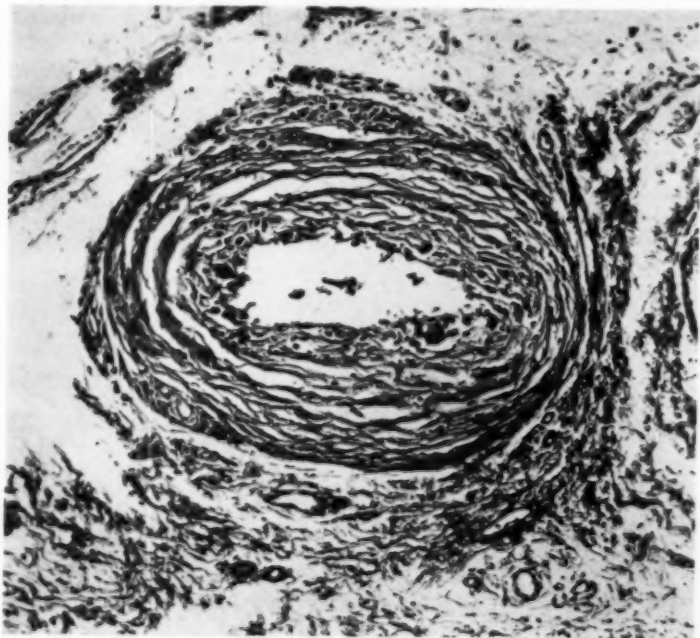


FIG. 6. Small subcutaneous artery. H & E  $\times 220$ . Note marked proliferation of fibroblasts and reticular cells in subintimal connective tissue with formation of multinucleated giant cells. Edema and some fragmentation of media.

cylinders (figures 7a and 7b). Irregular beading and varicosity of the axis cylinders and collections of corpora amylacea were found within the substance of the nerves.

#### DISCUSSION

The onset in our patient was characterized by pain, as in the original case of Kussmaul and Maier.<sup>3</sup> Griffith and Vural<sup>18</sup> also found pain to be one of the most common symptoms in their 16 cases. Logue and Mullins,<sup>21</sup> in their analysis of 177 cases, mention 43 clinical findings, with abdominal pain being fourth in the top five and occurring with a frequency of 56 per cent. The other four were: fever, 81 per cent; leukocytosis, 73 per cent; albuminuria, 65 per cent; hypertension, 56 per cent.

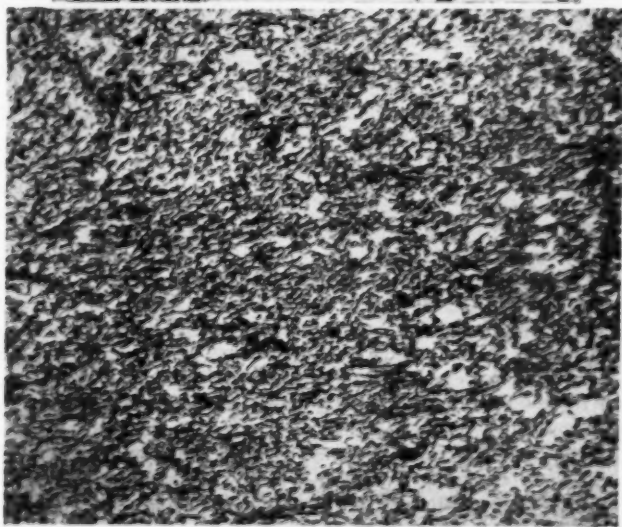
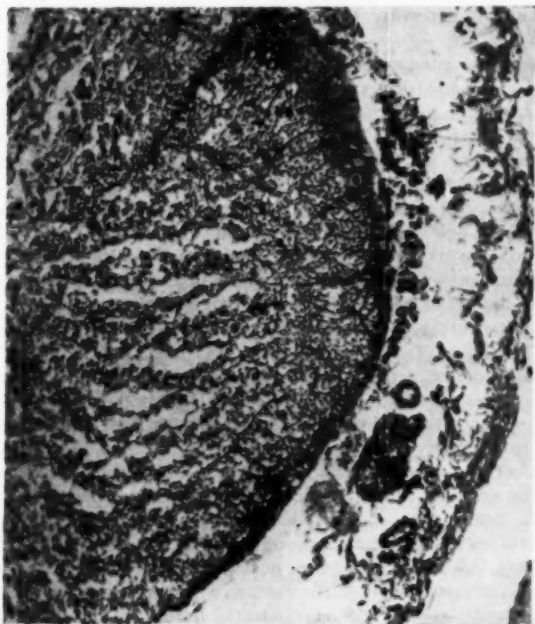


FIG. 7a. (above) H & E  $\times 150$ . Cross section of the left eighth cranial nerve, showing ischemic degeneration of the entire nerve. *b.* (below) H & E  $\times 150$ . Oblique cross section of the right eighth cranial nerve at the lateral aspect of the pontomedullary junction, showing ischemic degeneration of the nerve with fragmentation and varicosity of the axis cylinders. Corpora amylacea are present.

Skin lesions, as in our case, are not unusual. Ketron<sup>27</sup> studied more than 200 patients with polyarteritis nodosa and found cutaneous manifestations in 25 per cent, purpura being the most common. Logue and Mullins<sup>21</sup> found purpura or petechiae in 27 per cent of 177 cases, and other cutaneous manifestations in the absence of purpura in 4 per cent. These include erythematous, vesicular, urticarial and scarlatiniform eruptions. Ulceration of the purpuric lesions is not unusual.<sup>28</sup> Rose et al.<sup>23</sup> state that skin findings are of little aid in arriving at a correct diagnosis unless nodules are present. Ketron<sup>27</sup> points out that deep biopsies of skin lesions must be done to obtain arteries large enough to show the characteristic pathology. They believe that the vessels of the upper layers of the cutis are too small. The skin lesion that we removed deeply at necropsy showed the panarteritis much better than any of the shallower specimens taken during life.

Involvement of the nervous system is well known in this disease. Lovshin and Kernohan<sup>29</sup> studied 29 cases and found peripheral neuritis at some time during the course of the illness in 15, or 52 per cent. It was predominantly of the motor type; sensory findings, however, were common (13 out of 15 cases). They found nerve degeneration due to occlusion of the nutrient arteries, and not to some unknown toxin or pathologic agent which causes the arterial lesions and acts upon the nerves independently, as previously theorized by some.

The central nervous system was involved in 20 per cent of 300 cases reviewed by Foster and Malamud.<sup>30</sup> Nerve deafness was noted in two individuals. Parker and Kernohan<sup>31</sup> studied the central nervous system of 16 patients who died of polyarteritis nodosa and found arterial lesions in 11, or 69 per cent. All stages of the lesions were seen in varied locations; they were sometimes in the meningeal or cerebral vessels alone, or in both locations.

Gastrointestinal tract involvement, manifested by melena and pains, as observed in our patient, is not unusual. Arkin,<sup>8</sup> in 1930, listed involvement of the gastrointestinal tract as occurring in 50 per cent of the cases. Wold and Baggenstoss<sup>32</sup> reviewed 30 recorded cases of polyarteritis nodosa who died from 1926 through 1946. Lesions were found distributed throughout the abdomen in 21, and usually caused pain at the site of involvement. They noted that any portion of the digestive tract might be affected, including the liver, mesentery, pancreas and gall-bladder. It is not uncommon for these patients to be operated upon because their symptoms simulate common surgical conditions, and the findings are too equivocal for evaluation.<sup>33</sup> Logue and Mullins<sup>21</sup> observed abdominal pain in 56 per cent of 177 cases, and hematemesis or bloody stools in 18 per cent.

Late hypertension, asthmatic attacks, and death by cerebral hemorrhage, all of which occurred in our patient, have been seen many times in polyarteritis nodosa. Unusual, however, aside from complete bilateral deafness, were the absence of fever, the fairly normal laboratory findings and the lack of involvement of the heart and kidneys.

Frequently in polyarteritis nodosa the leukocyte count is elevated with an increase in polymorphonuclear leukocytes. Rarely there is a leukopenia. If the white cell count is normal, there is more often than not a relative increase in polymorphonuclear neutrophils. A normocytic anemia is a common finding. On random examination of the blood, eosinophilia occurs in about 25 per cent of the cases and more often than that on repeated examinations.<sup>34</sup> Even in the absence of impairment of renal function, the urine examination often shows

albumin, casts, and red and white blood cells.<sup>24</sup> Often, as Krupp<sup>24</sup> has reported, the urinary sediment shows the findings of all stages of glomerulonephritis. Usually the serum globulin is slightly increased and the albumin moderately decreased. In our patient there were no remarkable urinary changes or blood disturbances. Of 25 complete blood counts done over a period of three years, two showed an eosinophilia of 8 per cent. This was not considered significant, because of the extensive skin lesions. Histologic examinations of numerous skin and muscle specimens were not diagnostic. Blood, sputum and urine cultures were negative; microscopic examinations of the feces were non-contributory. Both a skin test and a complement fixation test for coccidioidomycosis were negative. Many serologic tests for syphilis were negative. The blood urea nitrogen three days before death was 23 mg. per cent.

The lack of involvement of the heart and kidneys is somewhat unusual for, as Arkin<sup>5</sup> found, they are the organs most commonly involved. He lists the frequency of occurrence in different organs as follows: kidneys, 80 per cent; heart, 70 per cent; liver, 65 per cent; gastrointestinal tract, 50 per cent; pancreas, 25 per cent; mesenteric arteries, 30 per cent; muscles, 30 per cent; peripheral nerves, 20 per cent, and the central nervous system, only 8 per cent; in contrast to Lovshin and Kernohan,<sup>29</sup> who found the peripheral nerves affected in 52 per cent of 29 cases, and Foster and Malamud,<sup>30</sup> who reported the central nervous system involved in 20 per cent of 300 cases.

Comparison of our case with that of Kussmaul and Maier<sup>3</sup> serves well to emphasize two of their most significant observations. These facts are fundamental in forming a correct concept about the disease. The first is that in a case severe enough to seek help there are usually more clinical findings than can be explained by any one well known syndrome. It was this observation that led Kussmaul and Maier<sup>3</sup> to discover "periarteritis nodosa." Spiegel<sup>35</sup> in 1936, after reviewing many cases, concluded that this was the most characteristic feature of the disease.

The variable clinical picture depends on the arteries involved; these are involved in no specific pattern. Of the approximately 500 cases reported, it is difficult to find any two alike.

The second observation is that clinical evidence of a healing process concurrent with a destructive one is commonly found. In the original case of Kussmaul and Maier it was quite evident in the neurologic changes of their patient. Certain muscles of this individual became paralyzed and then regained function temporarily, only to have paralysis recur.

In our patient this process was most strikingly demonstrated in the skin, although it was evident in the other organs involved. There were five distinct episodes of skin lesions; each lasted for from three to seven months, with remissions varying for from two to 12 months. At any specific time in a well established episode, all stages of lesions could be seen, from an acute, small, purpuric spot to a completely healed large ulcer of months' duration.

#### CONCLUSIONS

In any diagnostic problem where numerous diagnoses are suggested and there are no helpful laboratory findings, polyarteritis nodosa should be suspected. If close clinical observation reveals a healing process concurrent with a destructive one, this is further evidence in favor of the diagnosis of polyarteritis nodosa.

From the standpoint of the clinical picture anything can happen, including complete bilateral deafness. Polyarteritis nodosa is a relatively rare disease which has a clinical picture, with many changing facets and a cause which experimentation seems to suggest may be an unusual form of hypersensitivity due to almost anything.

Until there is better clarification of the etiology and better correlation between the experimental work in animals and the clinical picture, especially as to allergy, polyarteritis nodosa should be classified as a necrotizing panarteritis of undetermined etiology. The disease is characterized by a course that can be conveniently divided into three types. The first is mild, with reversible lesions and a good chance for spontaneous cure. Whether these include the hypersensitivity angiitides, as discussed by Zeek, Smith and Weeter,<sup>22</sup> we do not know. The second is more chronic and may go on for several years. In this type, nonvital structures can be extensively involved and show evidence of healing and recurrence, as in our case, and ultimate death due to spread to a vital structure. These, however, can also be chronically involved with exacerbations and remissions. In the third type, the course is acute and fulminating and rapidly progressive, until death occurs by destruction of a vital organ within two years.

#### SUMMARY

1. Polyarteritis nodosa causing complete bilateral deafness in a 51 year old white man is reported.
2. Historical, etiologic and pathologic concepts are briefly reviewed and the clinical findings discussed in relation to the case history presented.
3. A classification of polyarteritis nodosa based on prognosis is suggested.

#### ACKNOWLEDGMENTS

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#### BIBLIOGRAPHY

1. Matani: *De Aneurysmatis praecordium morbis*, Florenz, 1755.
2. von Rokitsansky, C.: *Denkschr. d. k. Akad. d. Wessenh.* 4: 49, 1852.
3. Kussmaul, A., and Maier, R.: *Über eine bisher nicht beschriebene eigentümliche Arterienkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitendes allgemeiner Muskellähmung einhergeht*, *Deutsches Arch. f. klin. Med.* 1: 484, 1866.
4. Ferrari, E.: *Ueber Polyarteriitis acute nodosa (sogenannte Periarteriitis nodosa) und ihre Beziehungen zur Polymyositis und Polyneuritis acute*, *Trieste, Beitr. z. path. Anat. u. z. allg. Path.* 34: 350-384, 1903.
5. Arkin, A.: *A clinical and pathological study of periarteritis nodosa*, *Am. J. Path.* 6: 401-426, 1930.
6. Rich, A. R., and Gregory, J. E.: *The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity*, *Bull. Johns Hopkins Hosp.* 72: 65-88, 1943.
7. Grant, R. T.: *Observations on periarteritis nodosa*, *Clin. Sc.* 4: 245-275, 1940.
8. Spiro, P.: *Zur Kenntnis des Wesens der Periarteritis nodosa*, *Virchows Arch. f. path. Anat.* 227: 1, 1919.

9. Gruber, G. B.: Zur pathologischen Anatomie der Periarteriitis nodosa, *Virchows Arch. f. path. Anat.* **245**: 123-127, 1923.
10. McCall, M., and Pennock, J. W.: Disseminated necrotizing vasculitis. The toxic origin of periarteriitis nodosa, *Am. J. M. Sc.* **206**: 652-659, 1943.
11. Ophuls, W.: Periarteriitis acuta nodosa, *Arch. Int. Med.* **32**: 870-898, 1923.
12. McCormick, R. V.: Periarteriitis occurring during propylthiouracil therapy, *J. A. M. A.* **144**: 1453-1454, 1950.
13. Selye, H.: Hormonal production of arthritis, *J. A. M. A.* **114**: 201-207, 1944.
14. Klinge, F.: Der Rheumatismus, *Ergebn. d. allg. Path. u. path. Anat.* **27**: 1-351, 1933.
15. Banks, B. M.: Is there a common denominator in scleroderma, dermatomyositis, disseminated lupus, Libman-Sacks syndrome, polyarteritis nodosa? *New England J. Med.* **225**: 433-444, 1941.
16. Klemperer, P.: The concept of collagen diseases, *Am. J. Path.* **26**: 505-519, 1950.
17. Klemperer, P.: The pathogenesis of lupus erythematosus and allied conditions, *Ann. Int. Med.* **28**: 1-11, 1948.
18. Griffith, G. C., and Vural, I. L.: Polyarteritis nodosa. A correlation of clinical and postmortem findings in seventeen cases, *Circulation* **3**: 481-491, 1951.
19. Sweeney, A. R., Sr., and Baggenstoss, A. H.: Pulmonary lesions of periarteriitis nodosa, *Proc. Staff Meet., Mayo Clin.* **24**: 35-43, 1949.
20. Horne, S. F., Curtin, A. C., and Kahn, E. A.: Splanchnicectomy for hypertension in lupus erythematosus and periarteriitis nodosa, *Ann. Int. Med.* **32**: 1202-1206, 1950.
21. Logue, B. R., and Mullins, F.: Polyarteritis nodosa. Report of eleven cases with a review of recent literature, *Ann. Int. Med.* **24**: 11-26, 1946.
22. Zeek, P. M., Smith, C. C., and Weeter, J. C.: Studies on periarteriitis nodosa, *Am. J. Path.* **24**: 889-897, 1948.
23. Rose, M. H., Littmann, D., and Houghton, J.: Polyarteritis nodosa. A clinical and pathological study and report of six cases, *Ann. Int. Med.* **32**: 1114-1143, 1950.
24. Baggenstoss, A. H., Schick, R. M., and Polley, H. F.: The effect of cortisone on the lesions of periarteriitis nodosa, *Am. J. Path.* **27**: 537-560, 1951.
25. Harrison, T. R.: Principles of internal medicine, 1950, the Blakiston Company, Philadelphia, p. 464-466.
26. Slinger, W. N., and Stock, V.: Cutaneous form of polyarteritis nodosa, *Arch. Dermat. and Syph.* **63**: 461-468, 1951.
27. Ketron, L. W.: Cutaneous manifestations of periarteriitis nodosa, *Arch. Dermat. and Syph.* **40**: 929-944, 1939.
28. Baehr, G.: The diseases of collagen, *Veterans Adm. Tech. Bull.* 10-74, May 31, 1951.
29. Lovshin, L. L., and Kernohan, J. W.: Peripheral neuritis in periarteriitis nodosa: a clinicopathologic study, *Proc. Staff Meet., Mayo Clin.* **24**: 48-52, 1949.
30. Foster, D. B., and Malamud, N.: Periarteriitis nodosa. A clinicopathologic report with special reference to the central nervous system. A preliminary report, *Univ. Hosp. Bull., Ann Arbor* **7**: 102-104, 1941.
31. Parker, H. L., and Kernohan, J. W.: The central nervous system in periarteriitis nodosa, *Proc. Staff Meet., Mayo Clin.* **24**: 43-48, 1949.
32. Wold, L. E., and Baggenstoss, A. H.: Gastro-intestinal lesions of periarteriitis nodosa, *Proc. Staff Meet., Mayo Clin.* **24**: 28-35, 1949.
33. Boyd, L. J.: Periarteriitis nodosa. Abdominal manifestations, *Bull. New York M. Coll., Flower and Fifth Ave. Hosps.* **4**: 27-32, 1941.
34. Krupp, M. A.: Urinary sediment in visceral angitis (periarteriitis nodosa, lupus erythematosus, Libman-Sacks "disease"), *Arch. Int. Med.* **71**: 54-61, 1943.
35. Spiegel, R.: Clinical aspects of periarteriitis nodosa, *Arch. Int. Med.* **58**: 933-1040, 1936.

## RECURRENT TUBERCULOUS PERICARDITIS\*

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SHOCK and pain are seldom considered to be prominent manifestations of tuberculous pericarditis. The onset of the disease is usually insidious, and pain, when present, has been most often reported as a dull ache, vaguely localized to the chest.<sup>1, 2, 3, 4, 5, 6, 7</sup> In the case to be reported the patient was a robust, stoical individual who, many times, presented himself with the sole complaint of agonizing chest pain.

## CASE REPORT

The patient, a 45 year old telephone lineman, was first seen on December 29, 1945, because of an upper respiratory infection associated with ill-defined precordial pain. His health had been excellent prior to this time, and the only significant fact in the past history was a two month period of intimate exposure to pulmonary tuberculosis in 1925. Physical examination was essentially negative, and an electrocardiogram (figure 1A) was within normal limits. He became asymptomatic without specific therapy and was able to resume full activities within a few days.

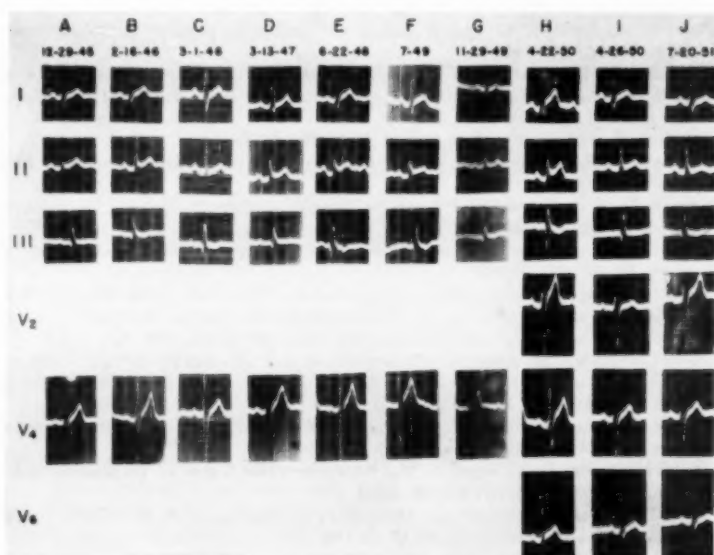


FIG. 1. A, B, D, E, F, and H coincide with episodes of severe chest pain. C, G, I and J coincide with periods during which the patient was asymptomatic.

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Two weeks later he experienced severe precordial pain radiating into the throat. Physical examination again was negative, but an electrocardiogram taken on this occasion (figure 1B) showed an elevation of the RS-T segment, most pronounced in Lead II. Symptoms disappeared spontaneously within 48 hours, and his electrocardiogram (figure 1C) returned to normal within two weeks.

One year later he experienced a recurrence of severe chest pain. This time a definite pericardial friction rub was heard in the second, third and fourth interspaces to the left of the sternum. The electrocardiogram again showed abnormalities of the RS-T segment (figure 1D).

In the subsequent four years he experienced, each year, two major and numerous minor attacks of precordial pain. Except for minor variations the pattern of these attacks was similar—the onset was usually sudden and frequently awakened him from a sound sleep; the pain was described as severe and steady, associated with a feeling of tightness in the chest and a "squeezing sensation" in the neck; it was located predominantly in the precordial region, although occasionally it originated in the left scapular region and radiated over the left shoulder and down over the left side of the chest anteriorly; it was aggravated by flexion of the trunk, by crossing the legs and sometimes by deep inspiration; it was not affected by exposure to cold, emotional upset or general physical exertion. The duration of the attacks was never longer than 48 hours. In the interval between these attacks he appeared normal and was able to carry on the strenuous duties of his occupation with no apparent difficulty.

On July 5, 1949, he was admitted to St. Luke's Hospital because of severe precordial pain. Except for slight electrocardiographic abnormalities (slight elevation of the RS-T segment, figure 1F), there were no significant physical or laboratory findings. Acute pericarditis and spontaneous mediastinal emphysema were considered as possible causes for the illness. The patient became asymptomatic and was discharged on the fourth hospital day. A definite diagnosis was not made.

On March 18, 1950, an appendectomy was performed for purulent appendicitis with perforation. The postoperative course was uneventful and there were no symptoms referable to the heart.

On April 22, 1950, he was again admitted to the hospital because of excruciating precordial pain. A total of 45 mg. of morphine sulfate and 400 mg. of meperidine hydrochloride (Demerol) in the five or six hours preceding admission resulted in only minimal relief. The patient appeared acutely ill. He was sweating profusely and had a grayish pallor. The rectal temperature was 38.7; pulse rate, 110; respiratory rate, 30, and blood pressure, 110/84 mm. of Hg. Breath sounds were absent over most of the pulmonary fields. The heart sounds were distant. No murmurs or friction rubs were audible. The abdomen was greatly distended and tympanitic. No ascitic fluid could be demonstrated and none of the abdominal viscera was palpable. There was no peripheral edema and no venous engorgement. The red blood count was 4,600,000 per cubic millimeter; hemoglobin, 14.7 gm.; white blood count, 14,000 per cubic millimeter; differential leukocyte count, normal; sedimentation rate (Wintrobe method), 37 mm. per hour. The non-protein nitrogen was 28 mg. per 100 c.c.; serum amylase (diastase), 29 Somogyi Folin-Wu units per 100 c.c.; serologic test for syphilis (Kline), negative. The urinalysis was normal. A roentgenogram of the chest showed an increase in cardiac size estimated at from 15 to 20 per cent above the expected normal, without definite evidence of pericardial effusion (figure 2A). On this and subsequent roentgenograms there was no evidence of pulmonary disease. An electrocardiogram showed a moderate Q wave in Lead III and definite elevation of the RS-T segment in Leads I, II, V<sub>2</sub> and V<sub>3</sub> (figure 1H). Despite the apparent severity of the illness and extreme shock, the patient rapidly became asymptomatic. Within four days the temperature became normal, the white blood count dropped to

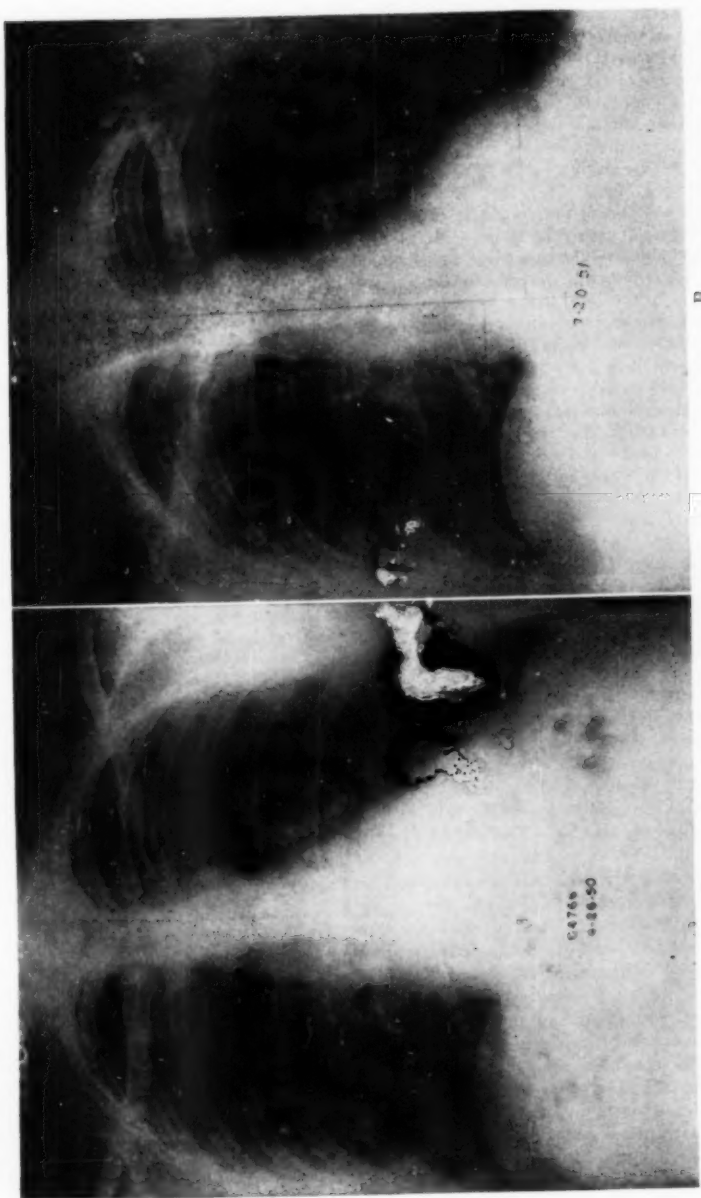


FIG. 2A. Roentgenogram of the chest taken April 26, 1950; maximal transverse diameter of the cardiac shadow 15.7 cm., 15 to 20 per cent above the expected normal. B. Roentgenogram of the chest taken July 20, 1951; maximal transverse diameter of the cardiac shadow 13.9 cm., normal.

8,000 and the electrocardiogram was normal (figure 11). He was discharged on the ninth hospital day with a final diagnosis of acute pericarditis, etiology undetermined.

Two days after his discharge he experienced a recurrence of pain and was admitted to the Cleveland Clinic. Clinical and laboratory data were essentially the same as during previous acute attacks. A second-strength tuberculin PPD skin test was slightly positive. On the seventh hospital day, after symptoms had subsided, a pericardial biopsy was obtained under local anesthesia. The external appearance of the pericardium was normal but the pericardial cavity was obliterated. The microscopic sections (figure 3) showed a connective tissue in part loose and in part densely sclerotic. There was moderate perivascular infiltration, with lymphocytes and occasional plasma cells. The vessels were engorged and foci of perivascular hemorrhage were present. There was no specific granulomatous inflammation. Acid-fast stains of the sections were negative. One month later, culture of the pericardial tissue was positive for *Mycobacterium tuberculosis*.

The patient was discharged to his home and for a three month period treatment consisted of absolute bed-rest, dihydrostreptomycin, 1 gm. daily, and para-aminosalicylic acid, 12 gm. daily. At the end of this period a roentgenogram of the chest showed a heart of normal size. The patient's activities were markedly restricted for another three months, and he was then permitted to return to light work. He remained asymptomatic for nearly a year. In May, 1951, he experienced slight precordial discomfort lasting for two days. Although clinical and laboratory examination showed no evidence of active disease, he was given streptomycin, 1 gm. twice weekly, and para-aminosalicylic acid, 12 gm. daily for a six month period.

#### DISCUSSION

Uncomplicated primary tuberculous pericarditis is a rare disease. Riesman<sup>8</sup> in 1901 used the term "clinically primary tuberculous pericarditis" to designate that form of the disease in which active tuberculous lesions could not be demonstrated elsewhere in the body at the onset of symptoms. Using this definition as their criterion, Stepmán and Owyang<sup>9</sup> in 1947 were able to collect 50 cases from the literature, to which they added three of their own. Although the case reported here may properly be included in this classification, it differs from previously reported cases in that this patient experienced recurrent attacks of severe chest pain.

The difficulties encountered in establishing a diagnosis of tuberculous pericarditis are well known. Suzman<sup>10</sup> reported a case of tuberculous pericarditis proved at autopsy in which, during life, the Mantoux test had been negative, the pericardial fluid repeatedly sterile on culture, and guinea pig inoculation negative on two occasions. Bacteriologic confirmation of the diagnosis in other reported cases<sup>6, 11, 12</sup> was equally difficult.

With the above facts in mind, it is apparent that every available method must be used if the etiology in a given case of pericarditis is to be established. Pericardial effusion fluid, when present, should be examined by smear, culture and guinea pig inoculation. Pneumopericardium, although not widely employed, may be an important adjunct in the diagnosis of tuberculous pericarditis.<sup>5, 6, 9, 11, 13</sup> It is thought that after production of a pneumopericardium the finding of a normal size heart and thickened pericardium on x-ray, plus the absence of murmurs on auscultation, points strongly to a tuberculous etiology.<sup>5, 9</sup> In cases of pericarditis without effusion, examination of the fluid is impossible—the production of a pneumopericardium is technically not feasible, and the advisability of a pericardial

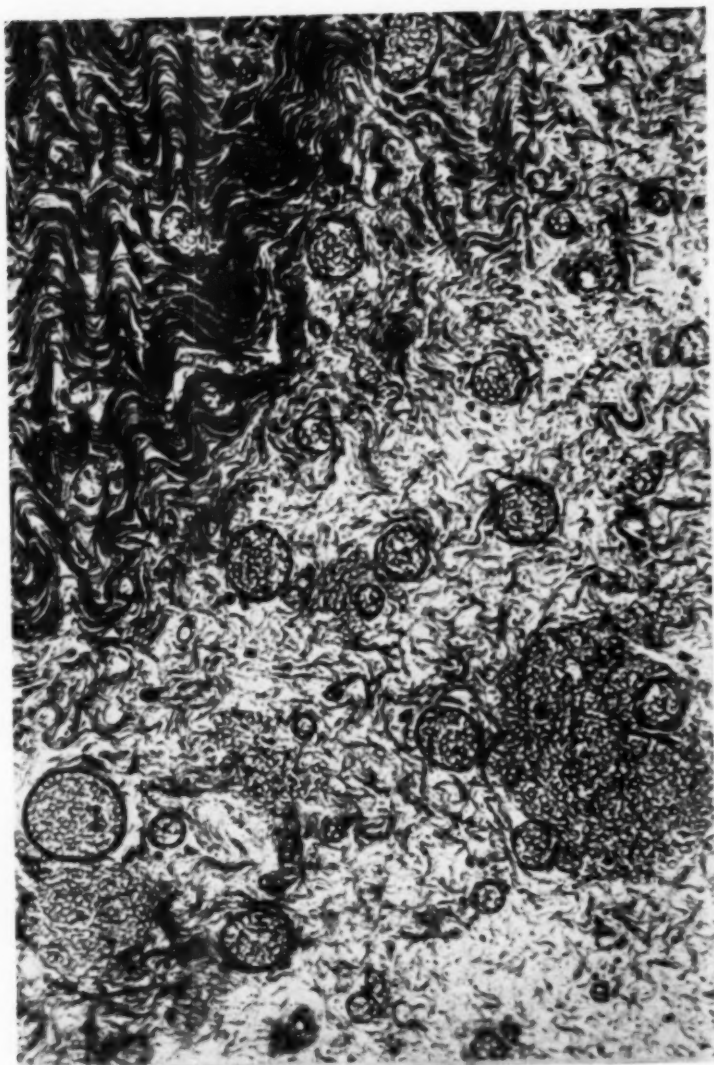


FIG. 3. High power view of the pericardium, showing proliferation and dilatation of the small blood vessels in the collagenous tissue.

biopsy should be considered. Effler has performed pericardial biopsies on eight cases of recurrent pericarditis.\* In two of these (one the case reported here), the diagnosis of tuberculosis was established by culture of the pericardial tissue.

The close similarity between the present case and the etiologically vague group of conditions which have been variously called acute benign pericarditis,<sup>14, 15, 16</sup> serofibrinous pericarditis secondary to acute pharyngitis,<sup>17, 18</sup> and acute non-specific or cryptic pericarditis<sup>19, 20</sup> raises the question as to whether some of these conditions are not instances of tuberculous pericarditis. Important distinguishing features of acute benign pericarditis are said to be: its occurrence in healthy young adults; its appearance following an upper respiratory tract infection; electrocardiographic changes of acute pericarditis which revert to normal within a period of one to six weeks, and frequently recurrent attacks.<sup>14, 19, 21</sup> All of the above findings were conspicuously present in the case reported here, and would seem to indicate that bacteriologic evidence is the sole means of differentiating adequately the two conditions.

#### SUMMARY

A case of recurrent pericarditis is reported in which *Mycobacterium tuberculosis* was isolated on culture of the pericardial tissue. The clinical course was characterized by repeated attacks of severe chest pain, and closely simulated reported cases of acute benign pericarditis. This similarity casts serious doubt on the validity of the latter diagnosis in some instances. To the present, a satisfactory clinical response appears to have been obtained with streptomycin therapy.

#### CONCLUSIONS

1. Tuberculous pericarditis may be characterized by severe recurrent chest pain.
2. The clinical course may be indistinguishable from so-called acute benign pericarditis.
3. Bacteriologic examination of the pericardial fluid or of pericardial biopsy tissue may be the sole means of differentiating the two conditions.
4. Advisability of pericardial biopsy should be considered in all cases of pericarditis which run a protracted course and in which the etiology is obscure.

#### BIBLIOGRAPHY

1. Burch, G. E., and Winsor, T.: Tuberculous pericarditis with effusion, *Clinics* 1: 166, 1942.
2. Thompson, W. P.: Primary tuberculosis of the pericardium, *J. A. M. A.* 100: 642, 1933.
3. Fine, M. J., and Katz, S.: Clinically primary tuberculosis of the pericardium, *Dis. of Chest* 10: 60, 1944.
4. Clarke, J. A., Jr.: Clinically primary tuberculous pericarditis, *Am. J. M. Sc.* 177: 115, 1929.
5. Heimann, H. L., and Binder, S.: Tuberculous pericarditis, *Brit. Heart J.* 2: 165, 1947.
6. Harvey, A. M., and Whitehill, M. R.: Tuberculous pericarditis, *Medicine* 16: 45, 1937.
7. White, P. D.: Chronic constrictive pericarditis, *Circulation* 4: 288, 1951.
8. Riesman, D.: Primary tuberculosis of the pericardium, *Am. J. M. Sc.* 122: 6, 1901.
9. Stepman, T. R., and Owyang, E.: Clinically primary tuberculous pericarditis, *Ann. Int. Med.* 27: 914, 1947.

\* A simple technic (employing local anesthesia) is utilized in obtaining pericardial tissue for histologic and bacteriologic examination. The technic is to be reported independently.

10. Suzman, S.: Tuberculous pericardial effusion, *Brit. Heart J.* **5**: 19, 1943.
11. Bellet, S., McMillan, T. M., and Gouley, B. A.: Tuberculous pericarditis, a clinical and pathologic study based on a series of seventeen cases, *M. Clin. North America* **18**: 201, 1934.
12. Barrett, A. M., and Cole, L.: A case of tuberculous pericarditis, *Brit. Heart J.* **6**: 185, 1944.
13. Giles, W. T.: A case of tuberculous pericarditis with effusion treated by means of pneumopericardium, *Am. Heart J.* **7**: 771, 1931-32.
14. Brown, M.: Acute benign pericarditis, *New England J. Med.* **18**: 666, 1951.
15. Talmage, W. G., and Succasunna, N. J.: Acute benign pericarditis, a report of two cases in young adults, *Am. Heart J.* **29**: 623, 1945.
16. Logue, R. B., and Wendkos, M. H.: Acute pericarditis of benign type, *Am. Heart J.* **36**: 587, 1948.
17. Willius, F. A.: Clinic on acute serofibrinous pericarditis secondary to acute pharyngitis, *Proc. Staff Meet., Mayo Clin.* **9**: 637, 1934.
18. Nathan, D. A., and Dathe, R. A.: Pericarditis with effusion following infections of the upper respiratory tract, *Am. Heart J.* **31**: 115, 1946.
19. Taubenhaus, M., and Brams, W. A.: Treatment of acute non-specific pericarditis with aureomycin, *J. A. M. A.* **142**: 973, 1950.
20. Pohl, A. W.: Acute pericarditis, a report of eight cases in which the etiology was "non-specific" or cryptic, *Ann. Int. Med.* **32**: 935, 1950.
21. Wolff, L.: Acute pericarditis simulating myocardial infarction, *New England J. Med.* **230**: 422, 1944.

### ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS IN THE NEGRO MALE: REPORT OF CASE WITH AUTOPSY FINDINGS \*

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REPORTS of the acute form of disseminated lupus erythematosus in the Negro race are few. Vessey and Nelson<sup>1</sup> reported the case of a 23 year old colored male with necropsy findings. This was the first report of the acute form of the disease in a colored male recorded in the North American literature. Kirby-Smith<sup>2</sup> recorded two cases of discoid lupus in Negro male youths. His photographs of the typical "butterfly" appearance of the facial skin lesions were classic. Pastor, Sloane and Goldburgh<sup>3</sup> reported necropsy findings in five male patients with acute disseminated lupus erythematosus, two of whom were colored males, one 12 years of age and the other 30. During the years 1935 to 1950, 12 patients with acute disseminated lupus erythematosus were autopsied at the Medical College of Virginia. Five of these were white females, six were Negro females and one was a white male.

The purpose of this note is to present an additional case of acute disseminated lupus erythematosus in the oldest Negro male to be recorded.

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## CASE REPORT

*History:* A 52 year old Negro male was admitted to the Ward Medical Service of the St. Philip's Hospital of the Medical College of Virginia on January 18, 1951. His chief complaint on admission was "weakness and joint pains for the past three months, and my skin broke out about a month ago." He had had pain and swelling in his left wrist and finger joints for three months, and his doctor had told him to have his teeth pulled and gave him some red liquid medicine. After having his teeth extracted, his fingers and wrist swelled and became more painful at intervals, and he was confined to bed because of weakness which progressed to such an extent that he was unable to walk without assistance.

About one month before admission he began having attacks of paroxysmal nocturnal dyspnea along with cough, thick sputum and slight ankle edema. His physician examined the sputum and requested a chest x-ray, neither of which was enlightening. He was given three "shots" which made him pass a good deal of water, and some digitalis pills of which he took one daily. Soon after this the skin of his face and neck began to "break out." The lesions first appeared on the bridge of his nose and across the cheeks and were raised and bluish-brown in appearance. Subsequently, the lesions progressed to involve the V-shaped area of his neck and armpits, as well as his back. As his skin lesions appeared his temperature became elevated and constitutional signs were prominent. His physician prescribed penicillin because of fever of 102° F. and râles in his lung bases; he also noted a marked hypochromic microcytic anemia of 6 gm. hemoglobin and a 2 plus proteinuria. At this time he had swelling of his eyelids and minimal swelling of the face. After his physician discovered a leukopenia he performed a sternal marrow aspiration, which was interpreted as being hypoplastic, so he referred the patient to the hospital for diagnostic study.

The patient's past medical history revealed that he had had a penile lesion 20 years before which had been treated with "pills and liquid medicine." He had never lost any time from his work as a laundry driver until four months before. There was no history of tuberculosis, and no history of excessive exposure to sunlight was elicited.

*Physical Examination:* On admission, the patient's temperature was 99° F., pulse was 66, and repeated blood pressure readings were around 140/80 mm. of Hg. The general appearance was that of a rather thin, wasted, chronically ill colored male appearing older than his stated age. There were dark, scaly, maculopapular, circular skin lesions, brownish purple in appearance and slightly indurated, over the bridge of his nose and the V-shaped area of his neck and the folds of the axillae. The lesions appeared to run in the lines of cleavage of the skin and were present over his back, shoulders and abdomen, and varied from 1 to 2 mm. in diameter. The only significantly enlarged lymph node, pea-sized and hard but freely movable, was located in the left epitrochlear region. There was a 5 cm. area of decubitus ulceration over the sacrum. Funduscopic examination showed marked A/V nicking and tortuosity of the arterioles of the left eye. There were two small hemorrhages in the right fundus. Examination of the chest showed only a few fine moist râles in both bases with slight dullness. The heart was not significantly enlarged, and a short blowing systolic murmur was heard at the apex. The rectal examination was negative except for black feces, which showed no blood on the guaiac test. The extremities showed a 1 plus edema of the ankles and pre-sacral area. The right arm had been amputated following a saw-mill accident many years previously.

*Laboratory Data:* Laboratory studies on admission revealed a hemoglobin of 7 gm., with 2.14 million red blood cells and 5,200 white blood cells. Peripheral differential blood smear showed 88 per cent granulocytes, with 9 per cent lymphocytes

and 3 per cent monocytes. The urine contained 1 plus albumin, with four to six white blood cells and one to two red blood cells, but a repeat examination showed 14 to 16 red blood cells per high power field. Serologic test for syphilis was positive to a titer of 1:4.

The sedimentation rate by the Wintrobe method was 74 and the non-protein nitrogen was 43 mg. per cent. The  $\text{CO}_2$  combining power and blood electrolytes were not abnormal. Total protein was 5.85 gm. per cent, with an albumin fraction of 1.18 gm.; another examination eight days later showed the total protein determination to be 5.9 gm., with 0.9 gm. albumin and 5.0 gm. globulin. The spinal fluid serologic test for syphilis was negative, with no cells and 20 mg. per cent protein. Numerous blood cultures were negative. An x-ray of the chest showed the heart within normal limits, and a skull film showed no changes. A film of the left wrist and fingers showed no markings indicative of arthritis. A barium enema was negative. The sternal marrow examination three days after admission showed polychromatophilia and a shift to the left of the granulocyte series. Bone marrow concentrate showed many typical lupus erythematosus cells (figure 1). A specimen of the patient's serum was

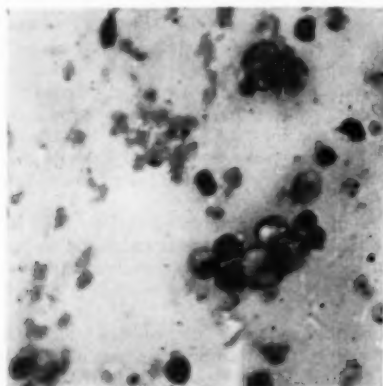


FIG. 1. Smear of bone marrow, showing lupus erythematosus cells.

mixed with normal bone marrow, and lupus erythematosus cells were demonstrated.

*Course in Hospital:* The patient continued to go downward. On the day after admission his temperature rose to  $102^{\circ}\text{F}$ . and fluctuated from normal to  $102^{\circ}$  every few days. A biopsy of the epitrochlear node was reported as showing "chronic lymphadenitis." In an attempt to cause an exacerbation of the skin rash, ultraviolet light exposure to the chest was given for 15 seconds one day and for 30 seconds on the next day, with possibly some increase in pigmentation of the rash but no other change. White blood counts varied from 5,200 to 12,000 with no evidence of eosinophilia. Since no cortisone or ACTH was available, the patient was placed on increasing doses of para-aminobenzoic acid, 1 to 3 gm. four times daily, without response. He finally became quite lethargic and breathless, with marked edema of his lower extremities. On the thirtieth hospital day his respirations became markedly diminished and labored, and no blood pressure was obtainable. He responded slightly to coramine and adrenalin but died soon afterwards.

*Autopsy Findings:* The appearance was that of an emaciated colored male who appeared older than the recorded age of 52 years. The skin over the bridge of the

nose, cheeks, neck and anterior as well as lateral chest revealed a macular type of hyperpigmentation, the individual lesions being slightly raised and ranging up to 1 cm. in diameter, with a tendency to confluency. An excavated decubitus ulcer, measuring 10 cm. in longest diameter, was noted over the sacrum, and smaller areas were seen in the regions of the lateral malleoli and right scapula. There was generalized dependent edema, especially marked in the lower halves of the legs.

The pericardial cavity contained approximately 100 c.c. of slightly red, turbid fluid. The pericardium was the "seat" of fibrinous inflammation, and presented the classic "bread-and-butter" appearance. The heart weighed 280 gm. The chambers were of normal size and shape. The valves were not remarkable. The left ventricular myocardium, on section, showed a few pale, tiny, 1 to 2 mm. foci. No fibrosis was evident.

In the pleural cavities there was clear straw-colored fluid, amounting to 600 c.c. on the right and 700 c.c. on the left. The pleurae were dull but no adhesions were detected. Scattered throughout all lobes of the lungs were seen small, miliary yellow nodules. In the midportion of the right upper lobe was a 2 cm. area of consolidation which contained many minute foci of necrosis.

The liver weighed 1,830 gm. and the spleen 50 gm. Throughout both organs, tiny foci of necrosis, 1 to 2 mm. in diameter, were easily discernible. The combined weight of the adrenals was 18 gm. On section they were not unusual.

The right and left kidneys weighed 180 gm. each. The capsules stripped with ease, revealing smooth underlying cortices. On section the cortical markings were indistinct, and the cortex presented a "blotchy" appearance, with focal areas of pallor and tiny white lesions identical with those observed in the lungs, liver and spleen.

The lymph glands deserve special mention. There was no appreciable generalized peripheral lymphadenopathy, but on section these structures contained clearly distinct spots of yellow necrosis. The medullae of the glands were edematous and prominent. The fat surrounding the lymph glands was pale, firm and adherent. These necrotic lesions were found in the glands of the neck, axillae, inguinal region, mediastinum, mesentery and para-aortic group. Permission to examine the central nervous system was refused.

Microscopically, the pericardium revealed deeply acidophilic collagen necrosis. The pericardium, pericardial fat and epicardium were all involved. The mesothelial cells of these structures were hyperplastic. Large, swollen fibroblasts lay in an edematous stroma. Plasma cells, lymphocytes, granulocytes and histiocytes made up the cellular inflammatory picture. Plasma cells particularly were prominent. Eosinophilic granulocytes were occasionally seen. The fibrinous pericarditis seen in some cases of acute rheumatic fever is identical to that seen here. Many of the coronary arteries contained subintimal nodules of fibrosis. Large foci of scattered necrosis, some with healing, were seen in the left ventricular myocardium. Masson's trichrome stains for connective tissue revealed para-arterial foci of scarring. Large bands of myocardial necrosis with replacement fibrosis were evident. The smaller arterioles within the myocardium were thickened with hyaline walls. Acid-fast stains and bacterial stains failed to reveal the presence of organisms. In the lungs, peculiar, discrete foci of necrosis were seen. These were characterized by centers composed of nuclei in all stages of disintegration. Bacterial and acid-fast stains failed to reveal any organisms in these necrotic masses. Around the periphery of the necrotic foci were compressed alveolar walls, thickened and converted to hyaline collagen masses. At the periphery of the necrotic areas arterioles with necrosis of the walls, sometimes containing tiny intraluminal thrombi, could be identified. Other arterioles had walls and adventitia heavily infiltrated with lymphocytes, plasma cells, neutrophilic granulocytes and the rare eosinophilic granulocyte. A rare giant cell was seen.

The pleurae showed edema, hyperplasia of the mesothelial cells and the presence of infiltration with lymphocytes, plasma cells and some granulocytes. Eosinophilic granulocytes were sparse. Many of the alveolar walls were thickened and converted to hyaline strands, the so-called fibrinoid thrombi. Focal areas of atelectasis were

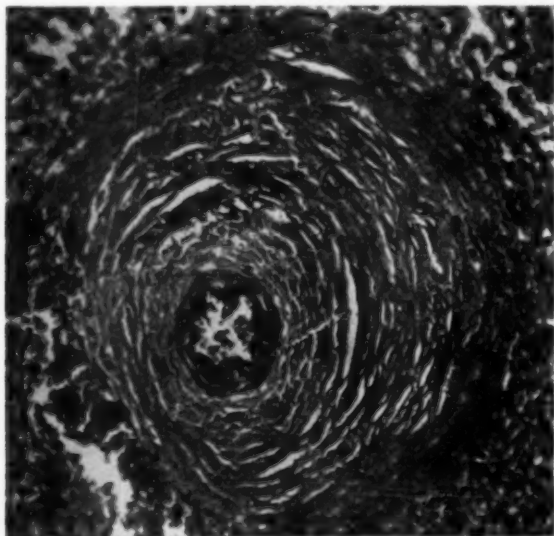


FIG. 2. Spleen. Periarterial fibrosis with "onion-skin" appearance.

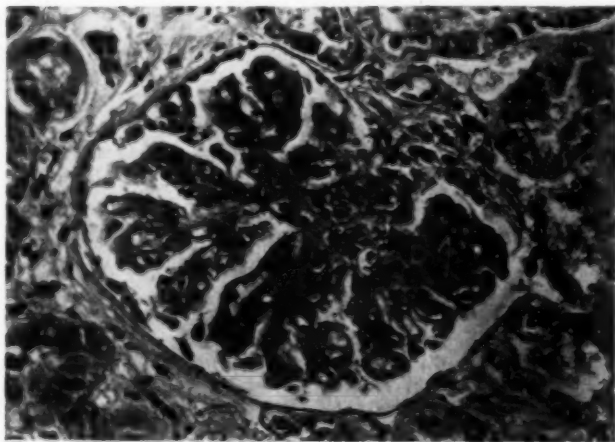


FIG. 3. "Wire-loops" in glomerulus.

seen here and there. Acute isolated areas of necrosis, similar to those seen in the lungs, were present in the liver. The sinusoids were greatly dilated and the cells showed prominent nucleoli and occasional mitotic figures. Several old, healed infarcts were evident. Arterioles were the "seat" of fibrinoid necrosis. Several "anemic foci" were seen. The pancreas was not histologically remarkable except for hyperplasia of the islets. The spleen presented focal areas of necrosis, periarterial fibrosis (figure 2) and hemosiderin deposits in the capsule, trabeculae and red pulp. The kidneys revealed the presence of "wire-loops" in the glomeruli (figure 3). Red cells and protein casts were seen in the loops of Henle. A small, tubular-type adenoma was present in the cortex of one kidney. The adrenals were not remarkable, except for loss of lipid throughout the cortex. Representative sections of skin revealed an atrophic epidermis, hyperkeratosis and ill-defined rete pegs. Necrotic arterioles were prominent in both the dermis and the subcutaneous tissue. Many foci of fat necrosis

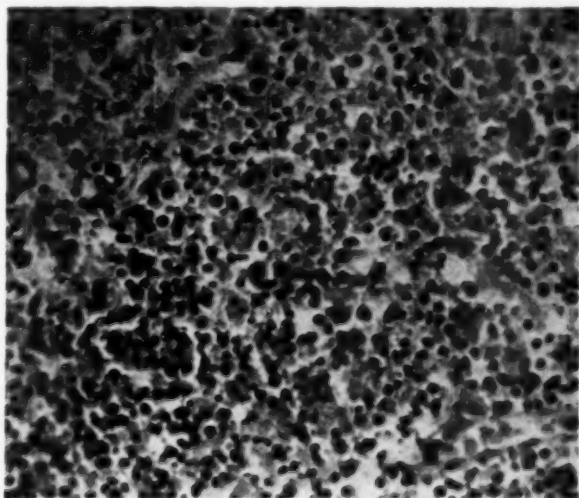


FIG. 4. Lymph gland necrosis, showing abundant fragmented nuclei.

were seen in the latter. The collagen of the dermis was hyalinized in thick acellular bundles. Numerous sections of both peripheral and deep lymph glands were studied. Foci of necrosis, identical with those observed in the lungs, liver and spleen, were seen in almost all of the glands (figure 4). Frequently the foci were small, while in other sections almost the whole gland was replaced by necrotic tissue. The bone marrow was not unusual. Throughout the striated musculature, necrotic arterioles were seen. Examination of the prostate revealed diffuse hyperplasia of the glandular elements. Necrosis of medium-sized arterioles, especially around the prostatic urethra, was easily demonstrated. Strikingly numerous were the necrotic testicular vessels. The probable cause of death was acute disseminated lupus, more specifically involving the pericardium.

**Anatomic Diagnosis:** Acute disseminated lupus erythematosus involving heart, lungs, liver, spleen, kidneys, lymph glands, striated musculature, testes, prostate.

## DISCUSSION

In recent years it has become evident that acute lupus erythematosus is seen more frequently in the male than was previously appreciated. This particular patient seems of interest because, from an examination of the literature, the occurrence of the disease in the older Negro male is rare. The presence of pericarditis, typical "butterfly" rash on the face, joint pains and L-E cells in the sternal marrow made the diagnosis obvious. The clinical onset in this patient was acute and the disease terminated rapidly. As more cases are recorded in the literature it will be interesting to see if the course in the male tends to be more acute than in the female. As in acute rheumatic fever affecting the heart, these patients may die as a result of a predominant pericarditis or myocarditis. This case showed a marked pericarditis, which undoubtedly contributed to the patient's death. It would seem advisable to emphasize the extensive lymph gland necrosis in this case. The necrosis may be confused with tuberculous necrosis but, unlike the latter, is not particularly characterized by giant cells and lacks its caseous appearance. Karyorrhexis is striking. Furthermore, a tendency to form distinct tubercles is absent. We have not found hematoxylin bodies of infallible diagnostic significance. The cause of the necrosis is arteriolar and capillary thrombosis.

## SUMMARY

1. A case of acute disseminated lupus erythematosus in a middle aged Negro male is reported.
2. The massive involvement of the lymph glands is considered unusual, and the value of their biopsy is emphasized as a useful diagnostic aid.
3. Attention is called to the pericarditis, which was probably the cause of death.

## BIBLIOGRAPHY

1. Vessey, J. M., and Nelson, H. G.: Acute disseminated lupus erythematosus: report of the disease in a Negro male, *Ann. Int. Med.* **32**: 565-571, 1950.
2. Kirby-Smith, J. L.: Erythematosus lupus in Negro youth, *J. Florida M. A.* **26**: 141-143, 1939.
3. Pastor, B. H., Sloane, N. G., and Goldburgh, H. L.: Disseminated lupus erythematosus in the male: report of five cases, *New England J. Med.* **244**: 81-84, 1951.

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**CLIMACTERIC OR "MENOPAUSAL" MUSCULAR DYSTROPHY:  
REPORT OF A CASE\***

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## I. INTRODUCTION

A SHORT time ago Shy and his co-workers in Montreal<sup>1</sup> clearly described, for the first time, the clinical features and response to cortisone therapy of a muscular disorder which first appears in the fifth or sixth decade of life. The

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terms "menopausal myopathy" or "menopausal muscular dystrophy" were coined by these investigators to describe a progressive, symmetrical weakness of the pelvic and shoulder girdle muscles. Patients with this disease characteristically complain of inability to rise from a chair unassisted, difficulty in climbing stairs, abrupt spontaneous falls and inability to raise the arms above the head. Since wasting is not evident early, and the deep reflexes remain intact, this syndrome may be mistaken for the general enfeeblement of age. Apparently the symptoms are reversible, for patients improve dramatically after the administration of vitamin E or cortisone.<sup>2,3</sup>

## II. REVIEW OF THE LITERATURE

Little reference can be found in the literature to primary degeneration of the voluntary muscles occurring during the fifth and sixth decades of life. In 1922 Bramwell<sup>4</sup> reported his observations of two patients, one a housewife, aged 53, the other a ploughman, aged 59, in whom symmetrical, atrophic and apparently progressive muscular palsies were found. The myopathy was limited to the quadriceps muscles and was accompanied by a quantitative reduction in the electrical excitability and a great diminution of patellar reflexes. No fibrillary twitches were observed, nor were there any sensory disturbances. These patients were unable to rise unassisted from a squatting posture.

Barnes<sup>5</sup> has described the adult members of a "myopathic family" who had a gradual atrophy and increasing weakness in the muscles of the pelvic girdle and lower extremities but retained powerful and well developed muscles of the shoulder girdle and arms. However, since these defects appeared in several members of the family long before the climacteric, and since many of them showed a pseudohypertrophic phase, these cases probably do not represent an example of the entity we are discussing.

In 1936 Nevin<sup>6</sup> collected from the literature 27 cases of muscular dystrophy occurring in late adult life. After careful clinical and histopathologic analysis he concluded that the findings in these instances were compatible with those of progressive muscular dystrophy. He then described two of his own elderly patients who had developed a muscular disorder which he considered a distinct clinical entity. One, a 68 year old housewife, had noted for seven years progressive weakness of the back, accompanied by difficulty in climbing stairs, raising her arms above her head and rising from a sitting position. Muscular wasting was present in the deltoid and biceps brachia muscles. There was varying weakness in all the muscles of the arms except the flexors of the fingers and the small muscles of the hands. The action of all the shoulder girdle muscles was very much reduced. In the legs there was wasting of the gluteal and thigh muscles. The weakness affected all the muscles of the limbs but was much more pronounced proximally. There was no evidence of fibrillation, hypertrophy or contracture. The deep reflexes were absent in the arms but present in the legs. There was no sensory loss. The second patient was a 58 year old woman who had complained for 12 months of gradually increasing weakness of her shoulder muscles. She too was unable to lift her arms above her head, had difficulty in combing her hair and could not bring her arms together in front of her. Walking became difficult and her legs tired easily. Examination of the muscular system was similar to that of the previous patient. Muscle biopsies were performed on both of these patients and histologically showed the changes later described by Shy.

## CASE REPORT

A 69 year old white man was admitted to Colorado General Hospital on September 27, 1951, complaining of weakness of his arms and legs and difficulty in swallowing for four months.

The patient had been well and able to work as a sheep-herder until approximately four months prior to admission, when he noted difficulty in rising from a chair, climbing stairs and raising his arms above his head. At the same time he began to have increasing difficulty in swallowing solid foods, which progressed until he was subsisting on a liquid and finely puréed diet; his weight had decreased from 155 to 142 pounds. He fell frequently when attempting to walk without assistance.

The patient's past history was unremarkable. He was unable to recall the causes of his parents' or grandparents' deaths, but was certain that there was no family history of any muscular disorders. His five siblings and five children were all in good health.

Physical examination showed a well developed, rather poorly nourished elderly Spanish-American man who was able to walk only a few steps at a time with a waddling, shuffling, uncertain gait. He was unable to raise himself unassisted either from a chair or from a supine to a sitting position in bed. He could not lift his arms above the horizontal, yet there was normal strength in his hand grip bilaterally. Marked wasting was present in the deltoid muscles, particularly on the left and, to a lesser degree, in the gluteus and quadriceps muscles bilaterally. The intrinsic muscles of the hands and feet appeared normal. Tendon reflexes were diminished but equal bilaterally and no pathologic reflexes were elicited. No evidence of cerebellar dysfunction was noted. Cranial nerves appeared intact and, despite the dys-



FIG. 1. Biopsy specimen before therapy started. Longitudinal section of muscle.

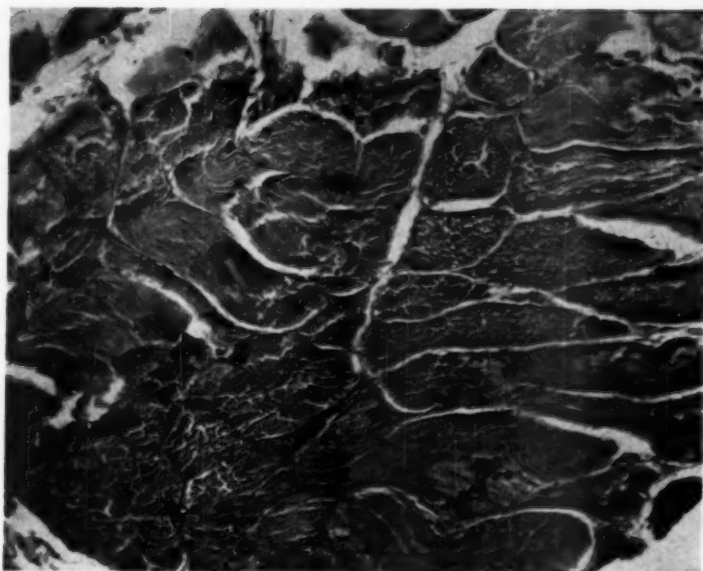


FIG. 2. Biopsy specimen before therapy started. Cross-section of muscle.

phagia, the palate lifted symmetrically. Pain, temperature, position and vibratory sense were all unimpaired.

Laboratory findings revealed a negative urinalysis and normal blood count and morphology. Blood chemistry determinations showed the following: fasting blood sugar, 98 mg. per cent; non-protein nitrogen, 28 mg. per cent; creatinine, 1.1 mg. per cent; total plasma proteins, 6.12 gm.; albumin, 3.06; globulin, 3.06; serum sodium, 135 mEq.; potassium, 4.3 mEq. The blood Wassermann test was positive on several occasions, with quantitative Kahn positive in a dilution of 1:10. Cerebrospinal fluid studies for cells, Kolmer's reaction and colloidal gold curve were negative; proteins, chlorides and glucose were within normal limits. Electrocardiograms were unremarkable.

Neither esophagoscopy nor roentgenograms of the esophagus and upper gastrointestinal tract demonstrated any obstructive lesion. However, fluoroscopic examination with a barium swallow disclosed a defect in the swallowing mechanism. The barium "pooled" in the oropharynx and, after a lag of a few moments, very slowly trickled down the esophagus.

Muscle power was graded by the department of physiotherapy; marked weakness of the deltoid, biceps, gluteus and quadriceps femoris muscles was recorded.

A biopsy of the deltoid muscle was performed on the fourteenth hospital day. Histologic studies revealed focal degeneration of muscle fibers, with varying degrees of necrosis in these areas, accompanied by phagocytosis and sarcolemmal proliferation. Round cell infiltration was present within muscle fibers but not in the interstitium. In some muscle fibers the only abnormality was loss of cross-striations (figures 1, 2 and 3). Since the microscopic findings were similar to those in Shy and McEachern's

description of "menopausal" muscular dystrophy, cortisone therapy was recommended for this patient.

On November 2, 1951, the daily injection of 100 mg. cortisone, intramuscularly in two depots, was started. After a week of steroid therapy the patient was able to rise from a chair and walked unaided. Within two weeks he was able to lift his arms above his head, although some limitation of motion of his shoulder joints persisted. During this period he also showed striking improvement in his ability to swallow, and after three weeks of cortisone he was eating all solid foods with ease. Fluoroscopy was repeated on his twentieth treatment day and, in contrast to the previous examination, the barium now passed from the oropharynx to the esophagus without delay. Muscle tests, repeated at weekly intervals, showed a progressive increase in strength of those muscles most affected initially.

The cortisone dosage was decreased to 50 mg. daily on the thirty-third treatment day, to 25 mg. on the forty-fourth day and discontinued on the fiftieth day. Six days prior to the discontinuance of cortisone, oral administration of alphatocopherol, 75 mg. daily, was started. The patient showed no tendency to relapse on tocopherol. Two days before discharge he was able for the first time to lift himself from a supine to a sitting position in bed, and a final muscle test revealed further gain in muscle strength.

A muscle biopsy was again secured when the cortisone administration was completed; histologic sections showed none of the areas of degeneration previously described (figure 4). It is possible that this marked change may have been due to an error of sampling. However, the areas of degeneration were so numerous in the original sections that we believe the second biopsy represented real change as the result of treatment.



FIG. 3. Biopsy before therapy started. Higher magnification.

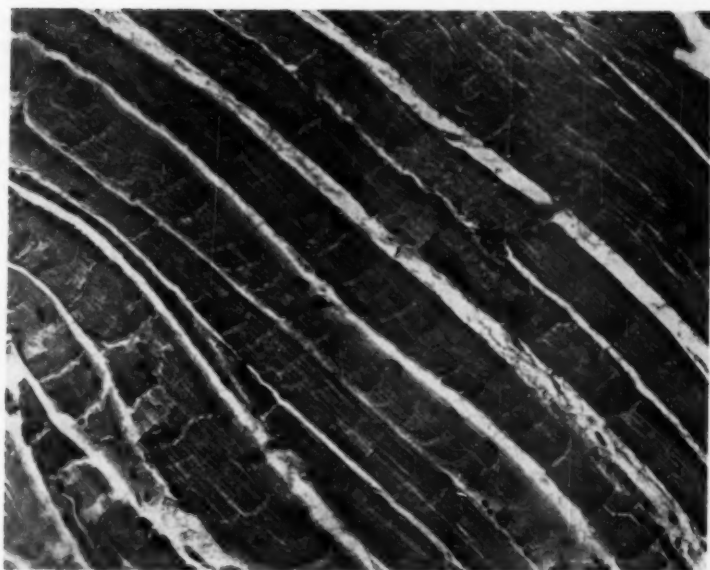


FIG. 4. Biopsy of muscle after 50 days of cortisone therapy.

The patient showed no adverse reactions to cortisone or tocopherol. During the course of therapy non-protein nitrogen, fasting blood sugar, serum sodium and serum potassium values remained at control levels. The blood pressure did not rise, the urinary output did not decrease, and there was no evidence of edema formation. The pattern of the electrocardiograms remained unchanged. As the patient's ability to swallow solid foods improved he gained weight steadily, from 133 pounds to 149 pounds. He was discharged on his fifty-sixth hospital day on a regimen of oral alpha-tocopherol, 75 mg. daily.

### III. ETIOLOGY

As with other muscular dystrophies, the origin of climacteric muscular dystrophy is not known. Neither Bramwell nor Nevin attempted to discuss this aspect of the disease. Heredity does not seem to play a part. Shy<sup>7</sup> believes that the relationship of this condition to the climacteric is significant, and implies that a steroid metabolic factor may be involved in precipitating the syndrome. He further states that, of the many types of myopathies treated with wheat germ oil, the most consistent response was shown by patients with this dystrophy.

### IV. PATHOLOGY

Malanud<sup>9</sup> and Pappenheimer,<sup>10, 11</sup> in studying young rats deficient in vitamin E, have observed histologic changes in striated muscle which closely resemble the lesions described by Nevin and Shy and are unlike those found in any of the other muscular dystrophies.

The outstanding histopathologic feature in climacteric muscular dystrophy is the finding of focal areas of muscle fiber degeneration throughout the microscopic section. In these regions the sarcolemmal cells are increased in number and are larger and paler than normal; accompanying them are accumulations of phagocytic cells within the muscle fibers.

The foci of necrosis may be surrounded by entirely normal muscle fibers, but within the focus itself the fibers are broken up into irregular and sometimes hyaline masses, associated with the cellular infiltrates which represent both sarcolemmal nuclei and phagocytic cells. The picture differs from that of myositis in that there is an absence of interstitial and perivascular infiltration. According to Nevin, the earliest evidence of muscular degeneration is seen in those fibers which demonstrate only a slight narrowing and marked increase in the number of sarcolemmal nuclei, with no loss of normal cross-striations. In the more advanced lesions of the disease there may be considerable replacement of muscle substance by fat and connective tissue, making it indistinguishable from other muscular dystrophies.

Shy and McEachern differentiate the muscle lesions of dystrophies from those of neurogenic muscular atrophies principally on the basis of the distribution of degenerated fibers. In the atrophic muscle, groups of fibers representing "motor units" show the characteristic degenerative changes. In the dystrophies, on the other hand, the changes are more focal and in the early stages involve only isolated muscle fibers surrounded by normal, unaffected muscle. In addition, necrosis, phagocytosis and loss of cross-striations occur earlier in the dystrophies and later in the neural atrophies.

As noted previously, the lesions found in the muscles of patients with climacteric muscular dystrophy are identical to those described in vitamin E deficient animals. Recently, however, Malamud and his group have found changes in the spinal cords of these animals, most marked in the dorsal columns, which clinically do not seem to occur in this group of human patients.

#### V. CLINICAL PICTURE

The onset of this condition is insidious. One of the earliest symptoms is a tendency to unpredictable falls caused by the legs suddenly collapsing. The individual may still be able to walk for some distance on level ground; however, as the condition advances the falls become increasingly incapacitating. Inability to rise from a supine position is another early sign. Progressive weakness of the shoulder girdle and hip muscles usually follows, causing difficulty in raising the arms above the head, bringing the arms together in front of the chest, and performing such acts as brushing garments. As the process continues, a waddling gait becomes evident and the patient can no longer climb stairs. The loss of strength is much greater in the proximal muscle groups than in the distal ones. Wasting does not keep pace with weakness and appears only in the later stages of the disorder, principally in the girdle musculature.

Examination of the individual muscles reveals marked weakness of the iliopsoas muscles, the quadriceps femoris group, the glutei and the adductors of the lower extremities. In the upper extremities the supraspinati, the infraspinati, the deltoids, serrati, triceps and biceps are usually most affected. On palpation the affected muscles seem soft and lacking in normal tonus and resilience. As

noted by Shy and McEachern<sup>7,8</sup> later, when fibrotic changes develop, the muscles become hard to palpation. Contractures are rarely seen.

Deep reflexes may be depressed in proportion to the severity of the involvement. Most of the muscles contributing to the tendon reflexes are relatively unaffected and hence the reflexes remain lively. The muscles supplied by the cranial nerves are usually not involved. The upper pharyngeal group, however, may become impaired, and dysphagia has been noted. There is no sensory impairment, and pain is not a prominent feature.

#### VI. THERAPY

Nevin's attempt to treat his two patients with glycine was entirely without success and their condition progressed unchecked. It was not until Rabinovich and his co-workers recognized the similarity between the lesion of menopausal muscular dystrophy and that of vitamin E deficiency in animals, and treated five patients with wheat germ oil, that any reversal of the clinical picture was obtained. This group of workers gave their patients an oral dosage of wheat germ oil equivalent to 65 mg. of mixed tocopherols daily, with very striking improvement in three of the five. All three patients showed a tendency to relapse when tocopherol was discontinued; therefore the drug had to be administered on a maintenance schedule to preserve improvement.

The most uniformly successful results have been obtained by Shy and his group<sup>1,12</sup> with the administration of cortisone. The drug was given in a dosage of 100 mg. daily in two intramuscular depots for 21 days, followed by a maintenance dose varying from 200 mg. weekly to 200 mg. every second day, depending upon the requirements of the individual. All of the patients relapsed within a week when a cholesterol placebo was substituted for the cortisone injections, but they were able to regain their improved muscular status when adequate therapy was resumed. Shy has found that oral cortisone serves as well as the intramuscular route, provided a dosage of approximately one and one-half times the intramuscular maintenance dose is given. Side effects of cortisone therapy have been dealt with as encountered, by means of a low sodium diet, diuretics and estrogen administration.

Although our patient was given cortisone for 50 days before alphotocopherol was substituted for the steroid, further clinical trial may show that an initial course of only two to four weeks of cortisone, 100 mg. intramuscularly daily, may be adequate preparation for the maintenance administration of alphotocopherol, 75 mg. daily orally. The weekly cost of this dosage of alphotocopherol is only approximately \$1.15, as against approximately \$9.00 a week for the average cortisone maintenance dose, so that the saving to the patient is considerable.

#### VII. DISCUSSION

Because of its late onset, climacteric muscular dystrophy is doubtless frequently mistaken for the general debility of old age; the disorder will be diagnosed only as it is recognized as a definite clinical entity. Since the first few cases were observed in women, Shy called the syndrome "menopausal muscular dystrophy." As more cases have been reported, however, it has become apparent that men are also affected, and therefore we feel that the term "climacteric muscular dystrophy" is more suitable.

Despite the occurrence of the dystrophy during the climacteric, no definite relationship to endocrine dysfunction has been established. Similarly, the resemblance between the pathology in this condition and that in experimental vitamin E deficiency merely suggests an analogy between the two, and further investigation will be needed before conclusions are warranted.

Unfortunately, none of the previous investigators procured muscle specimens following therapy. Therefore, evaluation of the apparently reversible organic changes which we noted in our second biopsy must await additional observation with similar histologic studies. The fact that, in some instances, dramatic improvement has been observed within a week after the initiation of therapy, and relapse within a few days after discontinuance, may indicate that functional changes precede organic ones in this dystrophy.

This disease relapses when cortisone therapy is discontinued. Therefore, it seems at the present time that again we are encountering the usual action of the adrenal steroids in producing a partial or complete remission of the clinical manifestations of a disease process without influencing the primary etiologic factor.

Because good results have been obtained in some cases with tocopherol, and because this drug is both less expensive and more innocuous than cortisone, it would seem worthwhile to try it for maintenance dosage in all cases of climacteric muscular dystrophy after an initial course of cortisone. Shy has stated that these patients require continued medication to the same extent that diabetics require continued insulin. Therefore, the drug of choice would be the least expensive and safest one that would maintain function at an optimal level.

The patient with climacteric muscular dystrophy is severely curtailed in his activity, suffers insidious, progressive weakness, and in the later stages of the disease may show irreversible fibrosis of muscle tissue. Therefore it is highly desirable that more physicians become familiar with the clinical features of this syndrome so that treatment may be instituted early.

#### SUMMARY

1. The literature on climacteric muscular dystrophy is reviewed.
2. The etiology, pathology, clinical picture and therapy of this syndrome are discussed.
3. A case treated with cortisone and alphatocopherol is presented.

#### BIBLIOGRAPHY

1. Shy, G. M., and McEachern, D.: The clinical features and response to cortisone of menopausal muscular dystrophy, *J. Neurol., Neurosurg. and Psychiat.* **14**: 101, 1951.
2. Shy, G. M., Brendler, S., Rabinovich, R., and McEachern, D.: Effects of cortisone in neuromuscular disorders, *J. A. M. A.* **144**: 1353, 1950.
3. Rabinovich, R., Gibson, W. C., and McEachern, D.: Neuromuscular disorders amenable to wheat germ oil therapy, *J. Neurol., Neurosurg. and Psychiat.* **14**: 95, 1951.
4. Bramwell, E.: Observations of myopathy, *Proc. Roy. Soc. Med.* **16**: 1, 1922.
5. Barnes, S.: A myopathic family with hypertrophic, pseudohypertrophic, atrophic, and terminal (distal in upper extremities) stages, *Brain* **55**: 1, 1932.
6. Nevin, S.: Two cases of muscular degeneration occurring in late adult life, with a review of the recorded cases of late progressive muscular dystrophy (late progressive myopathy), *Quart. J. Med.* **3**: 51, 1936.

7. Shy, G. M.: Personal communication.
8. McEachern, D.: Diseases and disorders of muscle function, *Bull. New York Acad. Med.* **27**: 3, 1951.
9. Malamud, N., Nelson, M. M., and Evans, H. M.: The effect of chronic vitamin E deficiency on the nervous system in the rat, *Ann. New York Acad. Sc.* **52**: 135, 1949.
10. Pappenheimer, A. M.: Muscular disorders associated with deficiency of vitamin E, *Physiol. Rev.* **23**: 37, 1943.
11. Pappenheimer, A. M.: The pathology of nutritional muscular dystrophy in young rats, *Am. J. Path.* **15**: 179, 1939.
12. Shy, G. M., and McEachern, D.: Further studies of the effects of cortisone and ACTH on neurological disorders, *Brain* **74**: 354, 1951.

## EDITORIAL

### *SARCOIDOSIS: RANDOM OBSERVATIONS*

THE publication of several recent surveys<sup>1, 2, 3</sup> of large groups of cases of sarcoidosis, either personally observed or collected from the literature, makes it possible now for the clinician to obtain a broad perspective of this interesting problem. Such a perspective should prove valuable not only in providing clues for further etiologic investigation, but also for a more rational approach to clinical management.

In common with the history of other diseases, the lesions of sarcoidosis first responsible for its recognition as a clinical entity, i.e. involvement of the skin and bones, seem now to be of relatively lesser importance in case finding. The high incidence of thoracic pathology in sarcoidosis, on the other hand, coupled with the widespread performance of routine chest x-rays will undoubtedly continue to expose many unsuspected cases. It is somewhat paradoxical that while the only firm basis for the diagnosis of sarcoidosis lies in the demonstration of the characteristic pathologic lesion, these lesions are by no means absolutely pathognomonic for the disease. Many diseases of known etiology produce tissue reactions closely resembling those of sarcoidosis. Much semantic confusion has occurred from the failure to make a careful distinction between the "sarcoid reaction" of such entities as leprosy, brucellosis, histoplasmosis, etc. and the disseminated disease, sarcoidosis. It is the opinion of most careful observers that despite the non-specificity of the tissue reaction, the concept that sarcoidosis is an entity or that it is due to a single etiologic agent is no way prejudiced.

Almost from the very beginning there has been a large body of opinion which has maintained that sarcoidosis is an aberrant form of tuberculosis due either to a variety of tubercle bacillus other than the human type, or to infection with an attenuated form of human tubercle bacillus, or invasion of an individual resistant or partially immune to this organism.<sup>4</sup> No useful purpose would be served in reviewing the numerous contributions to this aspect of the problem. Suffice it to say that there is no convincing evidence that any of these hypotheses is correct. There is no doubt, however, that tuberculosis does occur as a complication of some 15 to 25 per cent of cases of sarcoidosis. Attempts to incriminate the tubercle bacillus as the etiologic agent through immunological investigations have been equally unconvincing. A high percentage of patients with sarcoidosis, varying from 60 to 90 per cent in different series, has been found to be insensitive to the tuberculin test. This has been interpreted by the proponents of a tuberculous etiology

<sup>1</sup> Longcope, W. T., and Freiman, D. G.: A study of sarcoidosis, *Medicine* 31: 1, 1952.

<sup>2</sup> Freiman, D. G.: Sarcoidosis, *New England J. Med.* 239: 664, 709, 743, 1948.

<sup>3</sup> Ricker, W., and Clark, M.: Sarcoidosis. A clinico-pathological review of 300 cases, including 22 autopsies, *Am. J. Clin. Path.* 19: 725 1949.

<sup>4</sup> Pinner, M.: Non-caseating tuberculosis, *Am. Rev. Tuberc.* 37: 960, 1938.

as indicating a partially immune state of the patient with sarcoidosis. Yet patients with sarcoidosis who develop definite signs of active tuberculosis have been noted then to become tuberculin sensitive. Investigations by other immunologic technics—complement-fixation, the hemagglutination reaction of Middlebrook and Dubos<sup>5</sup>—have also failed to support the concept of tuberculosis as the etiologic factor.

Generalizations of all sorts seem to be particularly hazardous in a disease with such protean manifestations as sarcoidosis. The etiologic studies with reference to tuberculosis, cited above, are a case in point. Another is the factor of racial incidence. In the United States there is no doubt that sarcoidosis is more prevalent in negroes than in whites, yet a survey of the European literature fails to support such a racial predilection. A recent epidemiologic study of 226 cases of sarcoidosis in military personnel by Michael et al.<sup>6</sup> demonstrated that 88 per cent came from the southern United States. This was true for both negro and white groups. Even among the negro group those born in the South showed an incidence of 24.63 per 100,000 inductees, as compared to an incidence of 1.58 per 100,000 in those with a northern birthplace and 6.11 per 100,000 in those born in the west. A further difference was noted with regard to a rural or urban birthplace. The former predominated. Such provocative data, although incomplete, challenge the concept of the importance of a constitutional factor in sarcoidosis. On the other hand they lend credence to the idea that the predominance of negroes may be a regional factor and that the etiologic agent, whatever it is, is more heavily concentrated in the southern United States.

The active sarcoid lesion is a cellular tubercle composed of large, pale, epithelioid cells with associated prominent giant cells. The entire cellular mass often stands out in bold relief as an "inlay" in the midst of undistorted lymph node architecture or amidst the collagen fibers of the corium of the skin. The character of the process is essentially similar in all locations in the body and the size of the lesion depends largely on the number of individual "sarcoids." The clusters occur near small lymphatic channels (peribronchial, peri-vascular, subpleural, etc.). It is primarily an interstitial process and increase in size of the conglomerate lesion appears to depend on the number of individual granulomata. Functional impairment, when it occurs, is due to pressure and distortion. This is equally true for the alveoli of the lung and the articular surfaces of the finger joints. It is undoubtedly for this reason that sarcoidosis can exist for so long in the lungs without producing functional changes and can also cause severe distortions of the fingers without interfering with their function. Although complete resolution of sarcoid lesions seems possible on the basis of clinical evidence, the more common fate is healing by a process of fibrosis. The clinical pic-

<sup>5</sup> Fleming, J. W., Runyon, E. D., and Cummings, M. M.: An evaluation of the hemagglutination test for tuberculosis, *Am. J. Med.* 10: 704, 1951.

<sup>6</sup> Michael, M., Jr., Cole, R. M., Beeson, P. E., and Olson, B. J.: Sarcoidosis: preliminary report on a study of 350 cases with special reference to epidemiology, *Am. Rev. Tuberc.* 62: 403, 1950.

ture is apparently determined by the following factors: (a) location of lesion, (b) size of conglomerate masses, (c) complicating infection. In the main, the serious manifestations of the disease are due to mechanical interference with function.

Of particular interest is the presence of inclusions in the giant cells in approximately 30 per cent of the cases. These are of three types—asteroid or radial inclusion bodies, the so-called Schaumann body, and an irregular, poorly staining anisotropic fragment resembling a crystal or minute fragment of glass or silica. These are considered non-specific and not pathognomonic of the disease. The last type of inclusion is said to be more common in sarcoids of the skin and subcutaneous tissue, especially those associated with trauma. It is of interest that the so-called Schaumann body has also been observed in lesions resulting from exposure to beryllium compounds. Knowledge of the systemic manifestations of beryllium intoxication is of relatively recent origin, dating only from 1946.<sup>7</sup> In general, the clinical and pathological aspects of berylliosis, as known at present, differ from those of sarcoidosis. It seems likely, however, that additions to our clinical information regarding this subject will be forthcoming in the future.<sup>8</sup> The possible relationship to some form of sarcoidosis will be watched with interest.

The clinical course of sarcoidosis seems best described by the adjectives, variable, erratic, unpredictable. In many cases the time of onset of the disease can never be determined. It may be present without producing any clinical manifestations and be picked up by accident at autopsy or as a result of routine chest x-ray. In a series of 200 cases in army personnel reported by Ricker and Clark,<sup>3</sup> 42 or 14 per cent had fairly extensive pulmonary lesions on x-ray without clinical symptoms. From this asymptomatic extreme on the one hand, it is possible to jump to the other extreme in which marked pulmonary dysfunction, ocular difficulties, extensive skin and lymph node involvement are observed. Neither extreme is characteristic of the usual case of sarcoidosis. In the main, sarcoidosis might be characterized as a chronic process showing sluggish progression and widespread dissemination which heals slowly, relapses frequently, and harms largely by mechanical injury. It is difficult to know when and if recovery occurs. Conclusive evidence of recovery has rarely been obtained. In this regard, it is of interest to mention one of Boeck's original cases of sarcoid of the skin which was first observed in 1896 and died in 1940, at the age of 80, from a hypernephroma. At autopsy no trace of sarcoidosis was found anywhere.<sup>9</sup>

Sarcoid lesions which can be observed, such as those of the skin, may remain unchanged for years. Cases adequately followed over a long period

<sup>7</sup> Hardy, H. L., and Tabershaw, I. R.: Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds, *J. Indust. Hyg. and Toxicol.* **28**: 197, 1946.

<sup>8</sup> Sterner, J. H., and Eisenbud, M.: Epidemiology of beryllium intoxication, *Arch. Ind. Hyg. and Occup. Med.* **4**: 123, 1951.

<sup>9</sup> Danbolt, N.: Re-examination of Caesar Boeck's first patient with "multiple benign sarcoid of the skin," *Schweiz. med. Wchnschr.* **77**: 1149, 1947.

of time may show gradual spread from one site to another. Regression may occur in one area, while progression occurs in another. Serial chest x-rays have also permitted accurate observations of the course of pulmonary sarcoidosis. In a group of 37 such cases seen at the Massachusetts General Hospital,<sup>1</sup> 23 cleared up almost completely in a period of seven weeks to three years. Three patients in the group showed progression of the pathology. Eleven remained stationary during a period of observation ranging from three months to four years.

In the older literature on sarcoidosis, the dermatologic manifestations dominated the clinical picture. Now, this aspect of the disease occupies a relatively small rôle in the general clinical picture. In various series skin lesions occurred only in some 15 to 20 per cent of the cases. They are apparently more common in negroes and when present are almost always associated with other manifestations of the disease.

A survey of 92 autopsied cases<sup>1</sup> revealed pulmonary and lymph node involvement in 86 per cent, hepatic pathology in 65 per cent, splenic changes in 63 per cent, cardiac and renal implication in about 20 per cent. Of particular interest are the ocular manifestations of sarcoidosis. The incidence again varies in different series of cases, ranging from 8 to 64 per cent. Iritis and uveitis, the commonest lesions, may precede by months or years other manifestations of the disease. One ocular syndrome, uveo-parotid fever, described by Heerfordt in 1909, is regarded as a manifestation of widely disseminated disease in an active state. Cases of this type occur usually in young persons and are associated with systemic symptoms such as fever, malaise, gastrointestinal disturbances, joint pains, etc. Bilateral parotid swelling occurs in somewhat more than 50 per cent of the cases. Facial palsy occurs in perhaps a third of the cases and may be bilateral. The paresis is temporary and clears as the acute stage subsides in a period of several weeks to months. Although remarkably little evidence of hepatic dysfunction is noted clinically, this organ seems to be the seat of sarcoid lesions in a considerable percentage of cases. The increasing employment of punch biopsy of the liver, clinically, will undoubtedly provide more data on the incidence of hepatic pathology. In a recent study, Klatskin and Yesner<sup>10</sup> obtained pathological evidence of liver involvement in 15 biopsies in 15 patients.

Undoubtedly, the most serious aspects of sarcoidosis are seen in those cases in which cardio-pulmonary dysfunction occurs or in which serious ocular involvement results in blindness. For the most part, involvement of the heart occurs secondary to extensive pulmonary fibrosis. Occasionally instead of the syndrome of *cor pulmonale*, direct infiltration of the myocardium by sarcoidosis has been found. Pulmonary pathology is quite varied. The lesions may assume a disseminated miliary character, or con-

<sup>10</sup> Klatskin, G., and Yesner, R.: Hepatic manifestations of sarcoidosis and other granulomatous diseases: a study based on histological examination of tissue obtained by needle biopsy of the liver, *Yale J. Biol. and Med.* 23: 207, 1950.

sist of nodular infiltrations which later become confluent. Involvement of hilar nodes is quite common. The roentgen appearance is so variable that a positive diagnosis can usually be made only in conjunction with other findings. The lesions may remain stationary for months or years. They may recede or progress. Pleural effusions are rare.

Various metabolic changes occur in sarcoidosis, but again only in certain proportions of the cases. Among the commoner findings are moderate hyperglobulinemia and hypercalcemia. Hemolytic anemia, neutropenia, and thrombocytopenia have been reported in association with sarcoidosis of the spleen. Cystic changes in the small bones of the hands and feet, although commonly searched for, occur only in some 15 to 20 per cent of the cases.

Even a cursory survey of the protean character of sarcoidosis makes apparent the problem of evaluation of any therapeutic procedure in this disease. Until recently, all therapeutic measures seemed to possess little virtue. A series of reports on the effects of ACTH and cortisone on sarcoidosis has recently appeared.<sup>11, 12, 13</sup> There seems to be no doubt that objective and subjective improvement of various types of lesions has occurred under the influence of these hormones. Fresh lesions were more responsive than older ones. A considerable proportion, however, relapsed when therapy was terminated. These agents may provide a partial answer to the problem of prevention of serious ocular damage and improvement of respiratory dysfunction in sarcoidosis. Further evaluation, including the etiologic significance of the response, must await the accumulation of more data.

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<sup>11</sup> Sones, M., Israel, H. L., Dratman, M. B., and Frank, J. H.: Effects of cortisone in sarcoidosis, *N. England J. Med.* **244**: 209, 1951.

<sup>12</sup> Galdston, M., Weisenfeld, S., Benjamin, B., and Rosenbluth, M. B.: Effect of ACTH in chronic lung disease, *Am. J. Med.* **10**: 166, 1951.

<sup>13</sup> Silzbach, L. E.: Effects of cortisone in sarcoidosis: a study of 13 patients, *Am. J. Med.* **12**: 139, 1952.

## REVIEWS

### *Atlas of Tumor Pathology.*

- Tumors of the Peripheral Nervous System.* Section II, Fascicle 6. By ARTHUR PURDY STOUT, M.D., Professor of Surgery, Columbia University, College of Physicians and Surgeons, New York City. 57 pages; 60 cents. 1949.
- Teratomas.* Section III, Fascicle 9. By RUPERT A. WILLIS, D.Sc., M.D., F.R.C.P., Professor of Pathology, University of Leeds Medical School, Leeds, England. 58 pages; 50 cents. 1951.
- Tumors of the Mediastinum.* By HANS GEORGE SCHLUMBERGER, M.D., Professor of Pathology, Ohio State University, College of Medicine, Columbus, Ohio. 88 pages; 75 cents. 1951.
- Tumors of the Carotid Body and Related Structures (Chemoreceptor System).* Section IV, Fascicle 16. By PHILIP M. LeCOMPTE, M.D., Pathologist, Faulkner Hospital, Boston, Massachusetts, etc. 40 pages; 45 cents. 1951.
- Tumors of the Adrenal.* Section VIII, Fascicle 29. By HOWARD T. KARSNER, M.D., Medical Research Advisor, Bureau of Medicine and Surgery, U. S. Navy, etc. 60 pages; \$1.00. 1950.
- Tumors of the Breast.* Section IX, Fascicle 34. By FRED W. STEWART, M.D., Pathologist to Memorial Hospital, etc. 114 pages; \$1.10. 1950. Each section 26 x 20 cm. (paper-bound). Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C.

A good description of the Atlas is found in the Introduction: "An atlas of tumor pathology differs from a textbook in that it aims to give preëminently a pictorial representation of the many structural variants which characterize the many kinds of neoplasms." This fundamental principle is maintained throughout the fascicles already published. The Atlas is made up of a large number of fascicles (chapters), each published in a separate small paper-bound volume which can be grouped as desired. Although the fascicles are written by many authors, each tumor is considered in a uniform order. Each contributor states what he believes to be the truth and, for the sake of brevity, does not engage in lengthy discussions of controversial matters. All drafts of the individual contributors are submitted to a competent critic chosen by them and then are reviewed by the subcommittee as a whole, assuring to the reader the opinion of a number of pathologists.

There are 11 sections, each dealing with some generalized subject, such as "Tumors of the Skin and Cutaneous Melanomas," or "Tumors of the Lower Respiratory Tract and Thoracic Content." These sections are then broken down into several fascicles, making a total of 39 fascicles. For example: In Section VIII, *Tumors of the Urogenital System and Adrenals*, there are four fascicles with several subdivisions. Each fascicle takes up a subject, such as tumors of the adrenals, tumors of the kidneys, tumors of the bladder, etc., individually. Such fascicles are well illustrated with clinical photographs of gross pathologic specimens and many photomicrographs. The text is brief and descriptive, making it possible for the reader to obtain information about a given tumor quickly without having to peruse a lot of unnecessary reading.

Unfortunately, color photomicrographs are few because of the tremendous expense involved. However, the black-and-white photomicrographs are well done. This Atlas is an excellent reference book for pathologists as well as any clinician who is interested in improving his knowledge in the pathology of neoplasms. It is a valuable addition to the literature of tumors.

G. E. W.<sup>4</sup>

*Diabetic Glomerulosclerosis: The Specific Renal Disease of Diabetes Mellitus.* By HAROLD RIFKIN, M.D., F.A.C.P.; LOUIS LEITER, M.D., Ph.D.; and JAMES BERKMAN, M.D. 102 pages; 14.5 x 22.5 cm. Charles C. Thomas, Springfield, Illinois. 1952. Price, \$3.50.

This volume offers a critical summary of current knowledge of diabetic glomerulosclerosis based primarily on the authors' careful clinical and pathologic studies of an adequate number of patients over an adequate period of time. They stress the specificity of hyaline ball glomerular lesions and the lack of specificity of more diffuse lesions. They point out repeatedly the value of looking under a polarizing microscope for anisotropic fatty cells and casts in the sediment of acid urine freshly obtained from patients in whom the possibility of diabetic glomerulosclerosis may be entertained.

They detail the natural history of the clinical variants of the disease and the clinical and laboratory data available, and evaluate what has been written about the pathology and pathogenesis of this disease. A chapter on laboratory aids in diagnosis has photomicrographs of the same doubly refractile lipid casts and cells in ordinary and polarized light. Advice is given on the differential diagnosis of diabetic glomerulosclerosis in younger and older diabetic patients. The final section on treatment and possible prevention closes with the authors' request to physicians for further intensive study of patients who may develop this disorder.

This monograph, because of its detail and clarity, may be read with profit and pleasure by all physicians who in any capacity touch on the problems of patients with diabetes mellitus.

P. F.

*Rheumatic Diseases: Based on the Proceedings of the Seventh International Congress on Rheumatic Diseases.* Prepared by the Committee on Publications of The American Rheumatism Association, CHARLES H. SLOCUMB, M.D., Chairman; HOWARD F. POLLEY, M.D., WILLIAM D. ROBINSON, M.D., RICHARD T. SMITH, M.D., CHARLES RAGAN, M.D., EDWARD F. ROSENBERG, M.D., and CARLOS SACASA, M.D. 449 pages; 16.5 x 25.5 cm. W. B. Saunders Co., Philadelphia. 1952. Price, \$12.00.

This volume is a series of cases presented at the Seventh International Congress on Rheumatic Diseases held in New York City in 1949. The committee on publication has attempted to glean from the many articles originally presented, the best of the lot, and has set them up in an orderly fashion. Beginning with those articles relating to arthritis in general, there appear in sequence papers concerning rheumatoid arthritis, fibrositis, psychogenic rheumatism, osteoarthritis, newer concepts of therapy, and, finally, laboratory and investigative studies. Included in this array is the now classical paper of Hench and his collaborators on the use of cortisone in the treatment of rheumatoid arthritis. The dramatic effect of this work is lost by the lack of illustrations which highlighted the original presentation.

Other papers and discussions presented are both interesting and stimulating. For instance, two excellent articles on the increasing frequency of acute, early rheumatoid arthritides in older people, beyond the now accepted age group for the appearance of this disease; also the work on ACTH in gout and gouty arthritis.

The volume on the whole is well edited, and should prove an excellent reference to supplement the few existing texts on rheumatic diseases.

L. A. K.

*A Stereoscopic Atlas of Human Anatomy. Section I: The Central Nervous System—* in 4 volumes—with 34 View-Master Reels, and including a View-Master Stereoscope with light attachment and batteries. By DAVID L. BASSETT, M.D., Associate Professor of Anatomy, Stanford University, California. Approximately 500 pages; 17.5 × 21.5 cm. Sawyer's Inc., Portland, Oregon. 1952. Price: Section I—238 three-dimensional Kodachrome transparencies on 34 View-Master reels with 4 compact volumes containing over 500 pages of descriptive text and illustrations, \$27.50. Section I, as above, with the Sawyer \$2.00 View-Master without light attachment, \$29.50. Section I, as above, with the \$7.00 View-Master containing light attachment with transformer and cord for continuous lighting (for A.C. only), \$34.50.

The *Stereoscopic Atlas of the Central Nervous System* by Dr. Bassett will undoubtedly be hailed as a great advance in the use of visual aids in medical education. This Atlas must be seen to be fully appreciated. Words cannot describe the excellence of the views that reflect not only the great care exercised in selecting and preserving the original material, but also the well planned and skillful dissections. These have been photographed by a photographer who undoubtedly had abundant experience in color photography. The combination resulted in a beautiful series of stereoscopic pictures showing every stage of a very complete set of illustrations of the central nervous system. Practically every structure demonstrable by means of dissection has been covered in this Atlas.

The B.N.A. terminology has been used throughout. The stereoscopic photographs were not labeled directly, but key drawings were prepared as tracings from photographic enlargements of the original views. The drawings are adequately labeled and serve as labels for the photographs. The anatomist will find these views of step-by-step dissections, with each step preserved at the point of its greatest perfection, to have great value in teaching neuro-anatomy to medical students. The busy physician or surgeon desiring a short, quick review of topographical relations of structures of the central nervous system will find the ease of use and accessibility and clarity of detail ideal for their purpose, and will be able to review any dissection at a moment's notice. The extensive index makes it possible to examine a series of sections of any part of the central nervous system in which one may be interested.

There are in all, 238 three dimensional kodachrome transparencies in true full color. These show views of the general relationships of the brain and meninges within the cranial wall, dissections of the cerebrum, cerebellum, brain stem, and transverse sections of the brain stem. In many instances, cut surfaces are shown in relation to the remainder of the brain so that the location of nuclei on tracts can be correlated with surface features. There is one series of pictures on the exploration of the spinal cord and meninges in situ that is especially practical and valuable. Another series depicts radiographs of the brain, illustrating the various types of angiograms in various phases. A number of views, front and side views, were included in the latter series.

The Atlas will be of great value not only to beginning medical students, but to teachers of anatomy and educators in other departments of the medical school. It will be a boon to neurosurgeons and others desiring a concise, accurate, and graphic review of human anatomy. It will make it possible for practitioners to have the benefit of weeks of dissecting room demonstrations by simply devoting a single evening to the use of this Atlas. It is indeed a great contribution along the lines of improved efficiency in medical education skillfully executed and artistically presented. It will help to meet a growing need for telescoping courses in the medical curriculum. The Atlas may also be regarded as a step in the direction of the development of better methods of postgraduate medical self-education. These are all commendable, and it may be predicted that the Atlas will be widely used.

F. H. J. F.

*The Treatment of Injuries to the Nervous System.* By DONALD MUNRO, M.D., F.A.C.S. 284 pages; 16 × 24 cm. W. B. Saunders Co., Philadelphia, Pa. 1952. Price, \$7.50.

Dr. Donald Munro is an expert on the treatment of injury to the spinal cord. In this book the 115 page section devoted to spinal cord injury is well organized, well written and authoritative. That portion of the text concerned with cranio-cerebral trauma is concise and quite readable; but much abbreviated, often at the expense of accuracy. Some of the therapeutic recommendations would not be accepted outside the author's own clinic, as Dr. Munro himself suggests in the Preface.

There are abbreviated chapters on injury of peripheral and cranial nerves and of the autonomic nervous system. In addition there are three essays on rehabilitation, one by the vice-president of an insurance company.

This book probably will find varied use by medical students and house officers. The section devoted to the spinal cord can be enthusiastically recommended to all neurologists, orthopedic and neurologic surgeons and to the many whose skills are required in the successful treatment and rehabilitation of patients with spinal cord injuries.

R. M. N. C.

*Correlative Cardiology: An Integration of Cardiac Function and the Management of Cardiac Disease.* By CARL F. SHAFFER, M.D., F.A.C.P., and DON W. CHAPMAN, M.D., F.A.C.P., Baylor University College of Medicine. 525 pages; 16 × 24 cm. W. B. Saunders Co., Philadelphia and London. 1952. Price, \$9.50.

The authors designed this book to enable the student of cardiology to correlate various subjects that pertain to the diagnosis of heart disease, and "to comprehend the manifestations of the . . . cardiovascular system through simple, concise statements correlated with diagnostic illustrations." Toward this end they have gathered together their information and presented it in outline and table form, with many diagrams. The outline method of presentation makes reading difficult and uninteresting. It eliminates much of the discussion that should enable the intelligent student to weigh the facts properly and develop an understanding of the subject. The statements are too concise and resemble the notes one should take in preparing for an examination, rather than the reasoned text the student should study to understand the subject.

S. S.

#### BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Carbohydrate Metabolism: A Symposium on the Clinical and Biochemical Aspects of Carbohydrate Utilization in Health and Disease.* Edited by VICTOR A. NAJJAR. 134 pages; 22 × 14 cm. 1952. The Johns Hopkins Press, Baltimore. Price, \$4.00.

*Cornell Conferences on Therapy.* Volume 5. Edited by HARRY GOLD, M.D., Managing Editor; DAVID P. BARR, M.D., McKEEN CATTELL, M.D., FRANK C. FERGUSON, JR., M.D., FRANK GLENN, M.D., and GEORGE READER, M.D. 299 pages; 21 × 14 cm. 1952. The Macmillan Company, New York. Price, \$4.00.

*Essentials of Infant Feeding for Physicians: A Practical Text for Rapid Reference.*

By HERMAN FREDERIC MEYER, A.B., M.D., Assistant Professor, Department of Pediatrics, Northwestern University School of Medicine, etc. 252 pages; 23.5 × 15.5 cm. 1952. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$6.75.

*Great Adventures in Medicine.* Edited by SAMUEL RAPPORT and HELEN WRIGHT;

with an Introduction by DETLEV W. BRONK, President of The Johns Hopkins University. 874 pages; 21.5 × 14.5 cm. 1952. The Dial Press, New York. Price, \$5.00.

*Antoine Lavoisier, Scientist, Economist, Social Reformer.* By DOUGLAS McKIE,

D.Sc., Ph.D., Reader in the History of Science in the University of London. 440 pages; 21.5 × 14 cm. 1952. Henry Schuman, New York. Price, \$6.00.

*Lehrbuch der Röntgendiagnostik.* By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL and

E. UEHLINGER. 529 pages; 28.5 × 20 cm. (paper-bound). Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Broschiert DM 96.-

*The Mechanisms of Disease: A Study of the Autonomic Nervous System, the Endocrine System and the Electrolytes in Their Relationship to Clinical Medicine.*

By JOSEPH STAMBUL, M.D., Chief of the Cardiovascular Department of Albert Einstein Medical Center (Eastern Division), etc.; Foreword by GEORGE MORRIS PIERSOL, B.S., M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, etc. 746 pages; 23.5 × 15.5 cm. 1952. Froben Press, Inc., New York. Price, \$15.00.

*The Moral Theory of Behavior: A New Answer to the Enigma of Mental Illness.* By

FRANK R. BARTA, M.D., F.A.C.P., Director, Department of Psychiatry and Neurology, Creighton University School of Medicine and St. Joseph's Creighton Memorial Hospital, Omaha, Nebraska. 35 pages; 22.5 × 14.5 cm. (leather-bound). 1952. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$2.00.

*The 1952 Year Book of Medicine (May, 1951-May, 1952).* Edited by PAUL B.

BEESON, M.D., J. BURNS AMBERSON, M.D., WILLIAM B. CASTLE, M.D., TINSLEY R. HARRISON, M.D., GEORGE B. EUSTERMAN, M.D., and ROBERT H. WILLIAMS, M.D. 735 pages; 20 × 13.5 cm. 1952. The Year Book Publishers, Incorporated, Chicago. Price, \$6.00.

*Physiologie Normale et Pathologique du Métabolisme de L'Eau: Déshydratations—*

*Cedemes, Déséquilibres Hydriques.* By JEAN HAMBURGER and GEORGES MATHÉ. 502 pages; 25 × 16 cm. 1952. Éditions Médicales Flammarion, Paris. Price, 2,850 francs.

*The Prenatal Origin of Behavior: Porter Lectures, Series 18.* By DAVENPORT

HOOKE, Ph.D., Sc.D., Professor of Anatomy and Chairman of the Department, University of Pittsburgh School of Medicine. 143 pages; 21.5 × 14 cm. 1952. University of Kansas Press, Lawrence, Kansas. Price, \$2.50.

*Rheumatische Erkrankungen.* By PROF. DR. MAX HOCHREIN. 416 pages; 24.5 ×

17.5 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents in U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 36.-

- Roentgen-Diagnostics, Volume II: Skeleton (Part 2).* First American Edition (Based on the Fifth German Edition). By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL and E. UEHLINGER; English Translation Arranged and Edited by JAMES T. CASE, M.D., D.M.R.E., Professor Emeritus, Northwestern University Medical School, Chicago. 1,190 pages; 28 x 19 cm. (boxed). 1952. Grune & Stratton, New York. Price, \$45.00.
- Shock and Circulatory Homeostasis: Transactions of the First Conference, October 22-23, 1951, New York, New York.* Edited by HAROLD D. GREEN, M.D., Professor of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina. 245 pages; 23.5 x 15.5 cm. 1952. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$3.50.
- Symposium on Radiobiology: The Basic Aspects of Radiation Effects on Living Systems, Oberlin College, June 14-18, 1950; Sponsored by the National Research Council of the National Academy of Sciences.* Edited by JAMES J. NICKSON; Editorial Committee: P. MORRISON, M. BURTON, E. S. GUZMAN BARRON, G. FAILLA and H. M. PATT. 465 pages; 23.5 x 15 cm. 1952. John Wiley & Sons, Inc., New York. Price, \$7.50.
- Therapeutic Meal Plans: A New Diet Manual Prepared by The Department of Dietetics and Nutrition, University of Kansas School of Medicine.* Edited by VIRGINIA TOEWS, BERDENA ROSENOW and RUTH GORDON, Dietitians. 111 pages; 21.5 x 14 cm. 1952. University of Kansas Press, Lawrence, Kansas. Price, \$3.00.
- Der Tuberkuloseablauf im Körper.* By REINER W. MÜLLER. 170 pages; 25 x 17.5 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 24.-

## COLLEGE NEWS NOTES

### NEW LIFE MEMBERS

The College is pleased to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last list in the September issue of this journal:

Dr. Lee T. Pruitt, Beaumont, Tex.  
Dr. Robert Wilson, Jr., Charleston, S. C.  
Dr. Albert Waite Bryan, Madison, Wis.

### THE ATLANTIC CITY ANNUAL SESSION

The 34th Annual Session of the American College of Physicians is scheduled for Atlantic City, April 13-17, 1953, with general headquarters at Convention Hall and hotel headquarters at the Haddon Hall Hotel. Free, continuous bus service will be maintained between the hotel and Convention Hall. All first-class Atlantic City hotels have guaranteed a certain number of rooms for this convention and physicians may apply directly to the hotel of their choice. Official hotel reservation forms and maps will be distributed with the program but may be obtained in advance, if desired, by writing to the Executive Secretary of the College.

The program is essentially completed and will be published in full in the February 1953 issue of this journal. A special feature following the convention will be a post-convention cruise to Bermuda, leaving New York on Saturday, April 18, and returning to New York on Friday, April 24.

### AMERICAN COLLEGE OF PHYSICIANS POSTGRADUATE COURSES, SPRING, 1953

This announcement had to be released before final action has been taken by the Committee on Postgraduate Courses of the College, but the tentative schedule is as follows:

**PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE:** Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation, Cleveland, Ohio; A. Carlton Ernstene, M.D., F.A.C.P., Director; February 16-21, 1953.

**CARDIOVASCULAR DISEASE:** University of Southern California School of Medicine, Los Angeles, Calif.; George C. Griffith, M.D., F.A.C.P., Director; March 2-7, 1953.

**INTERNAL MEDICINE:** Mayo Clinic and Foundation, Rochester, Minn.; Drs. Arlie R. Barnes, F.A.C.P., Hugh R. Butt, F.A.C.P., Edgar V. Allen, F.A.C.P., and William H. Dearing, F.A.C.P., Co-directors; March 23-28, 1953.

**CARDIOVASCULAR DISEASE:** Philadelphia Institutions, Philadelphia, Pa.; William G. Leaman, M.D., F.A.C.P., Director; April 27-May 2, 1953.

**INTERNAL MEDICINE:** The Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M.D., F.A.C.P., Director; May 11-16, 1953.

**INTERNAL MEDICINE:** University of Oregon Medical School, Portland, Ore.; Howard P. Lewis, M.D., F.A.C.P., Director; May 18-22, 1953.

**ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION:** Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D. (Associate), Director.

**INTERNAL MEDICINE:** Cornell University Medical College and The New York Hospital, New York, N. Y.; David P. Barr, M.D., F.A.C.P., Director; Date to be determined.

It is anticipated that a detailed bulletin of the courses will be published in early January.

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#### AMERICAN COLLEGE OF PHYSICIANS REGIONAL MEETINGS

EASTERN PENNSYLVANIA, at Philadelphia, January 16, 1953  
COLORADO at Denver, February 17, 1953  
VIRGINIA at Hampton, February 26, 1953  
DELAWARE at Wilmington, February 27, 1953  
KANSAS at Kansas City, March 20, 1953  
NORTH DAKOTA at Fargo, September 12, 1953  
MIDWEST at Milwaukee, November 21, 1953

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#### VIRGINIA A.C.P. MEMBERS HOLD MEETING

The Virginia Section of the American College of Physicians held its Annual Business-Luncheon Meeting, Sept. 30 at Richmond, Va., during the three-day meeting of the Medical Society of Virginia. The Officers elected for 1952-53 were: Chairman of the Section, Dr. John B. McKee, F.A.C.P., Winchester; Secretary-Treasurer, Dr. J. Franklin Waddill, F.A.C.P., Norfolk.

Dr. Hugh R. Butt, F.A.C.P., of the Mayo Clinic, was a guest of the Section at this meeting. The meeting was addressed by Walter B. Martin, F.A.C.P., Norfolk, First Vice President of the College; Dr. Charles M. Caravati, F.A.C.P., Richmond, College Governor for Virginia; Dr. Byrd S. Leavell, F.A.C.P., Charlottesville, retiring Chairman of the Section; and Dr. J. Morrison Hutcheson, F.A.C.P., Richmond, ex-Governor and ex-Regent of the College.

Seventy-five members were present. The Winter Scientific Regional Meeting will be held at the Veterans Administration Hospital, Hampton, Va., Thursday, February 26, 1953.

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#### A.C.P. ELECTION OF MEMBERS

The next meetings of the College Committee on Credentials at which action will be taken on proposals for membership will be held Mar. 8 and Apr. 11, 1953. Proposals must be in the Executive Offices 60 days in advance of the meetings of the Committee. It is recommended that all proposals reach the College Governors 90 days in advance to allow them 30 days for local investigation.

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#### AMERICAN BOARD OF INTERNAL MEDICINE

The full personnel of the American Board of Internal Medicine, with indication of their representation of the American College of Physicians or the American Medical Association and the expiration year of their present appointments, follows: Current terms expire June 30 of the year indicated.

Walter L. Palmer, Chicago, Ill. (A.C.P., 1955), Chairman  
William B. Porter, Richmond, Va. (A.C.P., 1953), Vice Chairman  
Henry M. Thomas, Jr., Baltimore, Md. (A.M.A., 1955), Secretary-Treasurer  
Hugh R. Butt, Rochester, Minn. (A.M.A., 1955)  
Thomas M. Durant, Philadelphia, Pa. (A.C.P., 1954)  
Ray F. Farquharson, Toronto, Ont. (A.C.P., 1955)  
Thomas Findley, New Orleans, La. (A.M.A., 1955)  
Claude E. Forkner, New York, N. Y. (A.M.A., 1953)  
Chester M. Jones, Boston, Mass. (A.C.P., 1953)

Howard P. Lewis, Portland, Ore. (A.M.A., 1955)  
John Minor, Washington, D. C. (A.C.P., 1954)  
Albert M. Snell, Palo Alto, Calif. (A.C.P., 1953)  
Victor W. Logan, Rochester, N. Y., Librarian  
William A. Werrell, Madison, Wis., Executive Secretary-Treasurer

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#### EXAMINATIONS OF CERTIFYING BOARDS

The American Board of Internal Medicine held oral examinations at Philadelphia, Nov. 17-19. The next oral examination by this Board will be in Philadelphia in April, immediately preceding the Annual Session of the American College of Physicians. The probable dates are April 9-11, 1953.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa.

Written Examination—Jan. 16, 1953, under local monitors. This is the only written examination which will be given during 1953.

Oral Examinations—Baltimore, Md., Feb. 20-22, 1953  
Memphis, Tenn., Mar. 27-29, 1953  
Philadelphia, Pa., May 1-3, 1953  
Detroit or Ann Arbor, Mich., June, 1953  
Place undecided, Oct. 9-11, 1953 (Tentative)  
Indianapolis, Ind., Nov., 1953

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#### AMERICAN HEART ASSOCIATION ANNOUNCES RULES FOR FIRST ANNUAL HOWARD W. BLAKESLEE AWARD OF \$1,000.

The Howard W. Blakeslee Award of the American Heart Association has been set in the amount of \$1,000. In releasing the rules of competition, Dr. H. M. Marvin, Chairman of the Awards Committee, said the award has been established to encourage the best standards of scientific reporting, and will be given annually to the individual whose creative efforts have contributed most toward public understanding of the cardiovascular diseases in any medium of communication—including newspapers, magazines, books, radio, television or films. Material published or produced during the 1952 calendar year is eligible for consideration. Entries must be postmarked not later than January 15, 1953. The winner will be announced at the annual meeting of the American Heart Association, to be held in April, 1953, in Atlantic City.

Entry blanks and further information may be obtained from the Chairman, Managing Committee, Howard W. Blakeslee Award, American Heart Association, 44 East 23rd Stret, New York 10, N. Y.

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#### AMERICAN DIABETES ASSOCIATION OFFERS PRIZE FOR PAPER BY MEDICAL STUDENTS AND INTERNS

The American Diabetes Association offers a \$250.00 prize to medical students and interns for a paper on any subject relating to diabetes. The paper can be a report of original studies, a biographical or historical note, a case report with suitable comment, or a review of the literature.

Manuscripts must be submitted on or before April 1, 1953, to the Editorial Offices of DIABETES: the Journal of the American Diabetes Association, 11 West 42nd Street, New York 36, N. Y.

NATIONAL FOUNDATION FOR INFANTILE PARALYSIS ANNOUNCES  
CLINICAL FELLOWSHIPS

The National Foundation for Infantile Paralysis announces the availability of a limited number of postdoctoral clinical fellowships in physical medicine and rehabilitation to candidates who wish to become eligible for certification in that field. Fellowships will cover a period of one to three years at training centers which have been approved for residencies in physical medicine and rehabilitation. Stipends to Fellows are based on the individual need of each applicant. Selection of candidates will be made on a competitive basis by a Clinical Fellowship Committee composed of leaders in the field of medicine and professional education. In addition to these full-term fellowships, the National Foundation is making available a limited number of short-term fellowships to physicians who wish to become better acquainted with physical medicine and rehabilitation as it relates to their particular specialties.

Complete information concerning qualifications and applications on both types of fellowships may be obtained from the Division of Professional Education, the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y.

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FELLOWSHIPS IN INDUSTRIAL MEDICINE

The Institute of Industrial Health of the University of Cincinnati will accept applications for a limited number of fellowships offered to qualified candidates who wish to pursue a graduate course of instruction in preparation for the practice of Industrial Medicine. Any registered physician who is a graduate of a Class A medical School and who has completed satisfactorily at least two years of training in a hospital accredited by the American Medical Association may apply. (Service in the Armed Forces or private practice may be substituted for one year of training.)

During the first two years, the stipends for the fellowship vary, in accordance with the marital status of the individual, from \$2,100 to \$3,000. In the third year the candidate will be compensated for his service by the industry in which he is completing his training. Candidates who complete satisfactorily the course of study will be awarded the degree of Doctor of Industrial Medicine.

A one-year course, without stipend, is also offered to qualified applicants.

Requests for additional information should be addressed to the Institute of Industrial Health, College of Medicine, Eden and Bethesda, Cincinnati 19, Ohio.

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The United States Civil Service Commission has announced a Medical Officer examination for filling the position of Psychiatric Resident in Saint Elizabeths Hospital in Washington, D. C. The position pays \$3,400 to \$4,200. Education and training are required. No written test will be given. The maximum age limit is 35 years (waived for veterans).

Full information and application forms are available at most first- and second-class post offices, and at the U. S. Civil Service Commission, Washington 25, D. C. Applications will be accepted until further notice by the Executive Secretary, Board of U. S. Civil Service Examiners, Saint Elizabeths Hospital, Washington 25, D. C.

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Dr. W. P. Killingsworth, F.A.C.P., Port Arthur, was elected a Vice President and Dr. Charles D. Reece, F.A.C.P., Houston, was elected Treasurer of the Postgraduate Medical Assembly of South Texas at its eighteenth meeting.

Dr. John R. Danstrom (Associate), Oklahoma City, has been elected to a two-year term as Secretary-Treasurer of the Oklahoma State Radiological Society.

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Dr. Clayton B. Ethridge, F.A.C.P., was elected President of the Washington (D. C.) Heart Association at its annual meeting.

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Dr. Ko-Kuei Chen, F.A.C.P., Indianapolis, was awarded an honorary degree of Doctor of Science by the University of Wisconsin in June. Dr. Chen is President of the American Society for Pharmacology and Experimental Therapeutics, and a special consultant to the National Institutes of Health.

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Dr. Anton Julius Carlson, M.A.C.P., Chicago, and Dr. William Bosworth Castle, F.A.C.P., Boston, received honorary degrees of Doctor of Science at the 253rd Convocation of the University of Chicago on Oct. 3. As part of the Convocation, which was held in commemoration of the 25th anniversary of the Clinical Departments of the University, Medical Alumni Awards were bestowed on Dr. Henry W. Brosin, F.A.C.P., Pittsburgh; Dr. Victor Johnson, F.A.C.P., Rochester, Minn., and Dr. Chester S. Keefer, F.A.C.P., Boston, College Governor for Massachusetts.

Many Fellows of the College attended as delegates from medical schools and societies, with Dr. Howard Wakefield, College Governor for Northern Illinois, serving as the official representative of the College.

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At the annual fall clinical conference of the Oklahoma City Clinical Society, held Oct. 27-30, Dr. Roscoe L. Pullen, F.A.C.P., Houston; Dr. Joseph B. Vander Veer, F.A.C.P., Philadelphia, and Dr. Edwin L. Rippey, F.A.C.P., Dallas, were among the guest speakers. Dr. Pullen and Dr. Vander Veer discussed "Pulmonary Embolism, Treatment and End Result," and Dr. Rippey spoke on "Management of Complications in the Diabetic Patient." Dr. George F. Lull, F.A.C.P., Chicago, Secretary and General Manager of the American Medical Association, was the guest of honor at the banquet and spoke on "What Happens to Your American Medical Association Dues."

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Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia; Dr. Leon O. Jacobson, F.A.C.P., Chicago, and Dr. Cornelius P. Rhoads, F.A.C.P., New York, were three of the out-of-state speakers at the sixth annual meeting of the Southeastern States Cancer Seminar, held in Tampa, Fla., Oct. 30-Nov. 1. Dr. Chamberlain's subject was "Radiology," and Dr. Jacobson and Dr. Rhoads discussed "Chemotherapy."

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Dr. Louis N. Katz, F.A.C.P., Chicago, presented a paper entitled "Modern Concepts—Etiology and Pathogenesis of Arteriosclerosis" before the annual session of the Southwestern Medical Association at Albuquerque, N. M., Oct. 30-Nov. 1.

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Dr. Daniel A. Glomset, F.A.C.P., Des Moines, speaking on the "Philosophy of Adiposity," addressed the American Dietetic Association when the society convened for its annual meeting in Minneapolis, Oct. 21-24. Dr. Nathaniel E. Rossett, F.A.C.P., Memphis, discussed "Dietetic Management of Peptic Ulceration," and Dr. Sumner S. Cohen, F.A.C.P., Oak Terrace, Minn., used as his subject "Trends in Nutrition for

Patients with Pulmonary Tuberculosis." Dr. Priscilla White, F.A.C.P., Boston, presented a paper on "Newer Findings in Renalvascular Diseases," and Dr. Grace A. Goldsmith, F.A.C.P., New Orleans, collaborated in presenting "A Consideration of the Supranormal Dietary Requirements of Certain Acutely Ill Patients."

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Dr. Robert H. Williams, F.A.C.P., Seattle, Dr. William A. Winn, F.A.C.P., Springville, Calif., and Dr. John B. Doyle, F.A.C.P., Los Angeles, were among those who participated in the program of the annual meeting of the Association of Life Insurance Medical Directors of America, which was held in Los Angeles, Oct. 21-23. Their respective subjects were "Syncope, Vertigo, Dizziness"; "Coccidioidomycosis," and "Diseases of the Muscles and Neuromuscular Junctions." Also participating in the meeting were Dr. George C. Griffith, F.A.C.P., Los Angeles, who talked on "Problems in Borderline Cardiovascular Disease States," and Dr. Francis A. L. Mathewson, F.A.C.P., Winnipeg, Manitoba, who discussed "Prolonged P-R Interval in Apparently Healthy People."

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At the 25th anniversary dinner of the American School of Health Association, Dr. Howard A. Rusk, F.A.C.P., New York, delivered an address on "Crippled Children in a Crippled World." The dinner session was held during the 80th annual meeting of the American Public Health Association in Cleveland, Oct. 20-24. In the Food and Nutrition Section of the latter society, Dr. Norman Jolliffe, F.A.C.P., New York, was the moderator of a panel discussion on "Obesity—America's No. 1 Health Problem," and Dr. Leonard A. Scheele, F.A.C.P., The Surgeon General, United States Public Health Service, presided at the Joseph W. Mountin memorial session on "Advancing the Frontiers of Public Health."

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Under the Presidency of Dr. J. Harry Murphy, F.A.C.P., the Omaha Mid-West Clinical Society held its Twentieth Annual Assembly, Oct. 27-31, with headquarters at the Hotel Paxton in Omaha. Dr. Frank N. Allan, F.A.C.P., Boston, was one of the guest speakers. In addition to leading a discussion on "Problems in the Management of Diabetes," Dr. Allan spoke on "Diabetes in General Practice," on "Coma, Convulsions and Syncope" and on "Pitfalls in the Diagnosis and Treatment of Endocrine Disorders." Dr. Henry J. Tumen, F.A.C.P., Philadelphia, discussed "Treatment of Chronic Ulcerative Colitis," "Differential Diagnosis of Jaundice," and "Diagnosis of Pancreatic Carcinoma." Capt. Walter M. Simpson (MC), USNR (Retired), F.A.C.P., Laguna Beach, Calif., told of "Some Medical Experiences with the Allied Armed Forces in the South Pacific," and of "New Horizons in Cancer Control." Dr. Louis H. Clerf, F.A.C.P., Philadelphia, spoke on "The Esophagus and Its Diseases," "Significance of Hoarseness," and "Differential Diagnosis of Cough." Other guest speakers and their subjects included Dr. Burgess L. Gordon, F.A.C.P., Philadelphia, "The Physiologic and Clinical Aspects of Emphysema in Diagnosis and Treatment," and Dr. Odon F. von Werssowetz, F.A.C.P., Nashville, Tenn., "Rehabilitation of the Hemiplegic."

Members of the Executive Committee of the Society include, in addition to the President, Dr. Joseph D. McCarthy, A.C.P. Governor for Nebraska and Counselor of the Society, and Dr. Friedrich W. Niehaus, F.A.C.P., Omaha.

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"Medical Education in Cuba" was the title of the presentation made by Dr. Angel Vieta, F.A.C.P., Havana, at the 46th Annual Meeting of the Southern Medical Asso-

ciation, held last month in Miami. As guests of the Association, Dr. Henry L. Bockus, F.A.C.P., Philadelphia, presented a paper entitled "Acute Pancreatitis: Diagnosis and Treatment," and Dr. Howard Rusk, F.A.C.P., New York, discussed "Rehabilitation Following Cerebrovascular Accident." Dr. Paul A. O'Leary, F.A.C.P., Rochester, Minn., talked about "The Problem of Atopic Dermatitis," and Dr. Elmer L. Sevringhaus, F.A.C.P., Nutley, N. J., participated in round-table discussions on "Metabolic Problems in the Older Age Group of Patients" and "Present-Day Chemotherapeutic Agents of Value in Tuberculosis and in Malignancy."

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Dr. Wilburt C. Davison, F.A.C.P., Durham, N. C., was the first guest lecturer of the current series sponsored by the Naval Medical School. His talk which concerned changes in medical education and care, was delivered in Washington in late September. The series is sponsored annually by the School for the purpose of keeping members of the medical department abreast of the latest developments in medical treatment, research and care. Lectures are held on the last Friday of each month from September through May.

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Dr. Elmer Friedland, F.A.C.P., Buffalo, N. Y., was one of the out-of-state speakers at the annual Cancer Conference for Physicians, sponsored by the Rhode Island Medical Society and held in Pawtucket, Oct. 15. His topic was "Why Detection Clinics?"

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Dr. Charles F. Wilkinson, Jr., F.A.C.P., and Dr. Harry E. Ungerleider, F.A.C.P., New York, discussed, respectively, "Nonmalignant Lesions of the Pancreas" and "Insurance Aspects of Heart Disease" at the recent session of the Gulf Coast Clinical Society. The meeting was held in Pensacola, Fla., Oct. 16-17.

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Rear Admiral Lamont Pugh, (MC), USN, F.A.C.P., The Surgeon General, was the main speaker at the fiftieth anniversary celebration of the Naval Hospital Corps School, Portsmouth, Va., which occurred Sept. 20.

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At the joint meeting of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Trudeau Society, held in St. Louis, Oct. 16-18, Dr. John H. Skavlem, F.A.C.P., Cincinnati, spoke on "Research Dollars at Work."

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Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., addressed the annual fall meeting of the Northwestern Ohio Medical Association at Findlay, Oct. 8. His subject was "Headaches—General Considerations." Dr. Wright R. Adams, F.A.C.P., Chicago, another of the guest speakers, discussed "Cardiac Problems in General Practice," and Dr. David I. Rutledge, F.A.C.P., Boston, spoke on "Thyroid Diseases in General Practice."

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Under the joint auspices of the University of Puerto Rico Medical School and the Puerto Rico Medical Association, a round-table discussion on Manson's Bilharziasis was held October 9, 1952, at the auditorium of the Medical School, San Juan. Among those who collaborated were several members of the Expert Committee on Bilharziasis of the World Health Organization who were visiting the island at the time, and several members of the faculty of the Medical School. The participants were: Dr. Ernest Carroll Faust, Professor of Tropical Medicine and Hy-

giene, Tulane University of Louisiana; Dr. Willard H. Wright of the National Institutes of Health; Dr. Donald B. McMullen of the University of Oklahoma; Dr. Dyson M. Blair, Department of Health, Southern Rhodesia, Central Africa; Dr. Jose Oliver Gonzalez, Dr. Jose F. Maldonado, Dr. Enrique Koppisch, F.A.C.P., Dr. Rurico S. Diaz-Rivera, F.A.C.P., Dr. Jose Noya Benitez, all from the School of Medicine of the University of Puerto Rico. Dr. R. Rodriguez-Molina, F.A.C.P., Governor of the American College of Physicians for Puerto Rico, acted as moderator. The meeting was dedicated to Dr. Isaac Gonzalez-Martinez, who in 1904 first discovered the presence of Schistosomiasis Mansonii in the Western Hemisphere and in Puerto Rico, and who, 55 years after graduation from medical school, is still active in the practice of medicine in Puerto Rico.

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Dr. Cornelius P. Rhoads, F.A.C.P., New York, presented the second in a series of weekly cancer lectures sponsored by the Northwestern University Medical School. His topic on Oct. 15 was "Cancer Frontiers."

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Under the Presidency of Dr. Israel Davidsohn, F.A.C.P., Chicago, the American Society of Clinical Pathologists held a joint meeting with the College of American Pathologists in Chicago on Oct. 14. Dr. William S. Hoffman, F.A.C.P., Chicago, acted as moderator of the symposium on fluid and electrolyte balance in which Dr. Thaddeus S. Danowski, F.A.C.P., Pittsburgh, was one of the collaborators. Dr. Henry A. Schroeder, Sr., F.A.C.P., St. Louis, also made a presentation on fluid and electrolyte disturbances in internal medicine.

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Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn., delivered the annual Leo G. Rigler lecture at the University of Minnesota, Minneapolis, on Oct. 22. He discussed "X-Ray Diagnosis of Diseases of the Gallbladder."

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Dr. Louis F. Bishop, Jr., F.A.C.P., New York, spoke before the Geneva Academy of Medicine on "The Management of Cardiovascular Emergencies." The lecture, delivered Oct. 20, was sponsored by the Medical Society of the State of New York with the cooperation of the New York State Department of Health.

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Dr. Sol Parent, F.A.C.P., Newark, N. J., was one of the participants in the program of the National Rehabilitation Association. The theme of the annual meeting, which was held in Louisville, Oct. 19-23, was "Community Planning for Rehabilitation."

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Dr. Edward S. Orgain, Sr., F.A.C.P., Durham, N. C., and Dr. Howard B. Sprague, F.A.C.P., Boston, were two of the guest speakers at an all-day conference on cardiovascular disease, held at the University of Virginia, Charlottesville, Oct. 24. Their respective topics were "Management of Hypertension with Particular Reference to Newer Drug Therapy" and "Fear of Heart Disease."

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Under the Presidency of Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., College Regent, the Interstate Postgraduate Medical Association of North America held its Annual Assembly at Cleveland, November 10-13. Among those conducting clinics were Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, "Evaluation of Present Day Treatment of Peptic Ulcer"; Dr. Arthur M. Master, F.A.C.P., New York, "Cardiac Clinic"; Dr. John L. Garvey, F.A.C.P., Milwaukee, "Problems in Neurol-

ogy"; Dr. John M. Sheldon, F.A.C.P., Ann Arbor, "Place of Antihistaminics in the Treatment of Allergic Disorders"; Dr. William D. Robinson, F.A.C.P., Ann Arbor, "Present Day Treatment of Rheumatoid Arthritis," and Dr. Sturgis, "Evaluation of Some Recently Introduced Therapeutic Agents in Hematology."

Dr. Sturgis also addressed the Assembly on "The Changing Medical Scene"; other speakers and their topics included: Dr. Jonathan C. Meakins, M.A.C.P., Montreal, "Cardiac Asthma"; Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., "The Influence of Drugs on the Blood and Bone Marrow," and Dr. Milton W. Anderson (Associate), Rochester, Minn., "Valvular Heart Disease in Older People."

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Dr. Robert G. Bloch, F.A.C.P., New York, delivered the address at the luncheon session of the Philadelphia Tuberculosis Conference on Oct. 31, his topic being "The Effect of Drug Therapy on Tuberculosis Mortality and Morbidity." The Conference represented a joint meeting of the Eastern Section, American Trudeau Society; the Laennec Society of Philadelphia, and the Philadelphia Tuberculosis and Health Association.

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Dr. William L. Howell, F.A.C.P., Washington, D. C., was one of the collaborators on "The Antifoaming Effect of a Methylpolysiloxane Compound (DC Antifoam A) in Experimental Pulmonary Edema," which was presented at the fall meeting of the American Physiological Society, held in New Orleans, Sept. 5.

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Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, and Dr. J. Burns Amberson, F.A.C.P., New York, delivered two of the series of graduate medical lectures sponsored by the Department of Medicine, University of Virginia, Charlottesville. Dr. Curtis spoke Nov. 17 on "Sarcoidosis," and on Nov. 24 Dr. Amberson discussed "Management of Tuberculosis in View of Recent Advances."

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Under the Directorship of Col. Francis W. Pruitt, (MC), USA, F.A.C.P., "Current Trends in Internal Medicine" was presented at the Letterman Army Hospital, San Francisco, Oct. 20-24. Assisting Col. Pruitt on the committee in charge of the program were Dr. Dwight L. Wilbur, F.A.C.P., Col. Edward A. Cleve, (MC), USA (Associate), and Col. Byron E. Pollock, (MC), USA, F.A.C.P. The program was presented in coöperation with the faculties of the University of California School of Medicine and Stanford University School of Medicine, and the faculty included 22 members of the College.

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Dr. Edward L. Bortz, F.A.C.P., Philadelphia, College Regent, was the dinner speaker at the Geriatric Symposium sponsored jointly by the Veterans Administration Center, Kecoughtan, and the Virginia Peninsula Academy of Medicine, Sept. 18-19. His subject was "The Significance of the Increasing Life Span," and he later spoke on "Nutrition and Premature Aging." Dr. Willard O. Thompson, F.A.C.P., Chicago, another out-of-state speaker, discussed "Endocrine Aspects of Aging." Other participants on the program included Dr. Edward L. Alexander, Sr., F.A.C.P., and Dr. William A. Read, Sr., F.A.C.P., Newport News; Dr. Reno R. Porter, F.A.C.P., and Dr. William B. Porter, F.A.C.P., Richmond, and Dr. Harry Nushan (Associate), Kecoughtan.

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Under the guidance of Dr. Arthur J. Vorwald, F.A.C.P., the Seventh Saranac Symposium was held at Saranac Lake, N. Y., Sept. 22-26. Dr. Anthony J. Lanza,

F.A.C.P., New York, who delivered the Leroy U. Gardner Memorial Lecture, and Dr. O. A. Sander, F.A.C.P., Milwaukee, were members of a panel that discussed "Definitions and Clarification of Terms Pertaining to Pneumoconiosis." Dr. William S. McCann, F.A.C.P., Rochester, N. Y., was chairman of the group that discussed "Clinical Aspects of Pneumoconiosis," and Dr. James J. Waring, M.A.C.P., Denver, led the discussion on "Cardio-Circulatory Aspects of the Pneumoconioses." Dr. Kenneth M. Lynch, F.A.C.P., Charleston, S. C., talked on "Asbestos Weavers" at the session on "Pneumoconiosis and Pulmonary Cancer," with Dr. Cornelius P. Rhoads, F.A.C.P., New York, presiding. Dr. Lemuel C. McGee, F.A.C.P., Wilmington, College Governor for Delaware, presented a paper on "The Functions and Value of Medical Boards and Medical Examiners in Controverted Compensation Cases," and those who took part in the discussion that followed included Dr. Edgar Mayer, F.A.C.P., New York.

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Dr. S. S. Lichtman, F.A.C.P., New York, was one of the participants at the annual session of the National Gastroenterological Association at New York in October. The title of his paper, presented in the Symposium on Diseases of the Liver, was "The Present Status of Liver Function Tests."

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Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, was one of the discussants in a panel on "Political Editorials in Medical Journals," which was part of the program of the Sixth General Assembly of the World Medical Association when it met in Athens, Greece, Oct. 11-16. Dr. Moorman is Editor-in-Chief of the *Journal of the Oklahoma State Medical Association*.

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Dr. Bruce K. Wiseman, F.A.C.P., Columbus, Ohio, was one of the guest speakers at the annual meeting of the Indiana State Medical Association in Indianapolis, Oct. 28-30. He discussed "Problems and Dangers of Transfusion."

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Dr. Eugene A. Stead, Jr., F.A.C.P., Professor of Medicine at Duke University School of Medicine, spoke on "Dyspnea" before the House Officers' Association of New England Center Hospital, Boston, Nov. 19.

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Dr. Arthur M. Olsen, F.A.C.P., Dr. Howard F. Polley (Associate), and Dr. Charles H. Scheifley, F.A.C.P., all of Rochester, Minn., were among the guest speakers from the Mayo Clinic who participated in the Sixth Councilor District Postgraduate Day, held Oct. 29 in Youngstown, Ohio. Dr. Olsen and Dr. Polley spoke, respectively, on "Common Pulmonary Diseases" and "ACTH and Cortisone in Arthritis." Dr. Scheifley's two subjects were "ACTH and Cortisone in Rheumatic Fever" and "Treatment of Chronic Congestive Heart Failure."

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Dr. C. Sidney Burwell, F.A.C.P., Research Professor of Clinical Medicine at Harvard Medical School, spoke on "Constructive Pericarditis," Oct. 28, at the Madigan Army Hospital, Fort Lewis, Wash.

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Dr. Eugene B. Ferris, Jr., F.A.C.P., Cincinnati, and Dr. Robert W. Wilkins, F.A.C.P., Boston, were two of the guest speakers at the fourth annual symposium of the Washington Heart Association, held in Seattle, Nov. 7-8. Dr. Ferris and Dr. Wilkins were two of those who participated in discussions on "The Arrhythmias" and on "Hypertension."

Dr. Harold Feil, F.A.C.P., Cleveland, using "Surgical Approach to Heart Disease" as his topic, addressed the annual luncheon of the directors of the West Virginia Heart Association at Morgantown, Oct. 31.

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Dr. E. Grey Dimond, F.A.C.P., Kansas City, Kans., has recently been made Professor of Medicine and Chairman of the Department of Medicine, University of Kansas School of Medicine.

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Dr. George B. Jerzy Glass (Associate), New York, has been promoted to Associate Clinical Professor of Medicine at the New York Medical College and Associate Attending Physician at Flower and Fifth Avenue Hospitals.

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Dr. Alfred S. Dooneief (Associate), Bedford Hills, N. Y., has recently been appointed Attending Physician, Division of Pulmonary Diseases, Montefiore Hospital, New York.

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Dr. Hyman I. Goldstein (Associate), Camden, N. J., has recently been elected life-time Honorary Fellow of the National Gastroenterological Association and of the New Jersey Gastroenterological Society. Dr. Goldstein is also the Medical Historian of the two organizations.

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Dr. Wyndham B. Blanton, F.A.C.P., Richmond, has recently been appointed Assistant to the Dean, Medical College of Virginia.

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Dr. Rafael Rodriguez-Molina, F.A.C.P., Governor for Puerto Rico and Chief of Medical Service, Veterans Administration, San Patricio Hospital, San Juan, has been appointed Clinical Professor of Medicine at the new Medical School of the University of Puerto Rico.

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The Fifth Annual Harvard Lecture was delivered at the University of Colorado Medical Center on November 7 by Dr. Edward D. Churchill, John Homans Professor of Surgery, Harvard Medical School, and Chief of the Surgical Services at the Massachusetts General Hospital. His subject was "The Segmental Structure of the Lungs."

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Dr. Bernard Sternberg, F.A.C.P., Brooklyn, N. Y., has recently been appointed Clinical Assistant Professor of Medicine at the State University of New York College of Medicine at New York City.

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Dr. David Adlersberg, F.A.C.P., New York, has been promoted to Associate Physician for Metabolic Diseases at the Mount Sinai Hospital.

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Dr. Philip S. Hench, F.A.C.P., of Rochester, Minnesota, has been honored by the Mississippi Valley Medical Society as its Honor Award Recipient for 1952. The award, consisting of a gold medal and a certificate, was presented Dr. Hench at the banquet on the occasion of the 17th Annual Meeting of the Society at the Jefferson Hotel, St. Louis, Oct. 2. Dr. Hench is Professor of Medicine, Mayo Foundation, University of Minnesota and a 1950 Nobel Laureate in Physiology and Medicine.

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Dr. Eli H. Rubin, F.A.C.P., New York, was guest speaker and participated in clinics and conferences at the 26th Annual Refresher Course given by the Dalhousie University Faculty of Medicine, Halifax, Nova Scotia, October 20 to 24, 1952.

## OBITUARIES

## DR. JESS VARDEMAN BELL

Dr. Jess Vardeman Bell, F.A.C.P., died September 29, 1952, closing a career of unusual activity in educational effort and of outstanding service to his profession. His pre-medical education, terminating in the degree of A.B., was obtained at the University of Missouri. He received his doctorate in medicine at Northwestern University in 1920. After an internship at Michael Reese Hospital, Chicago, he joined the staff of Kansas City General Hospital, becoming Chief of Medicine in 1939 and continuing in that office until his death. He was successively Instructor, Associate and Assistant Professor of Medicine in the University of Kansas School of Medicine.

His contributions to organized medicine were numerous and important: founding member and past president, Kansas City Southwest Clinical Society; member, Jackson County Medical Society, Missouri State Medical Society, American Medical Association, Kansas City Internist Society, American Association of Life Insurance Medical Directors; former member, Chicago Medical Society, Illinois State Medical Society; Diplomate, American Board of Internal Medicine; member of Kappa Alpha and Nu Sigma Nu fraternities.

Besides this he was active in the interests of the American College of Physicians, of which he had been a Fellow since 1928, taking a leading part in the Regional Meeting held in Kansas City during the early months of World War II.

In addition to these medical interests, he was a man of considerable personal charm who impressed those who knew him intimately. His patients, his office associates and his colleagues miss him. He left a pattern to follow.

RALPH A. KINSELLA, M.D., F.A.C.P.,  
Governor for Missouri

## DR. GEORGE WALTER CRAMP

Dr. George Walter Cramp, F.A.C.P., died in Brooklyn, New York, on May 20, 1952.

Dr. Cramp was born in Brooklyn on April 19, 1896. He received his preliminary education in the schools of Brooklyn, and graduated from Colgate University with an A.B. degree in 1918, and from the Long Island College Hospital with a degree of M.D. in 1923; he later pursued postgraduate medical studies in Vienna.

He served as an intern at the Methodist Hospital, Brooklyn, from 1923 to 1925, where he later became Clinical Assistant in the Department of Internal Medicine, Assistant Roentgenologist, Attending Roentgenologist, and Director of the Department of Radiology. Dr. Cramp also served for two years at the Long Island College Hospital as Adjunct in Medicine in the Department of Cardiology, and later was Consultant Radiologist and Consulting Roentgenologist at St. Luke's Hospital in Newburgh, N. Y. For some time he was also Instructor in Radiology at the Long Island College of Medicine.

He participated in two World Wars, as Lieutenant in the United States Army, World War I, and in World War II he served from January, 1942 to March, 1946 in the Medical Corps of the United States Navy, in which he was separated from active service as a Captain. In World War II he served in the Pacific Theatre in the early days of the war.

He was a charter member of the Osler Digest Society, and a member of The Medical Club of Brooklyn. He was a member of Delta Kappa Epsilon and Alpha Kappa Kappa fraternities, and was also an active Mason. He was a member of the

Military Order of World Wars, Naval Order of the United States, the Association of Military Surgeons, and the Lawrence Lovell Post of the American Legion.

Dr. Cramp held membership in the state and local societies and was a member of the New York Postgraduate Hospital Roentgenological Society, Brooklyn Roentgen Ray Society, New York Gastro-enterological Society, New York Society of Approved Roentgenologists, Associated Physicians of Long Island, and the Radiological Society of North America. He was a Diplomate of the American Board of Radiology and a Fellow of the American College of Roentgenologists. He had been a Fellow of the American College of Physicians since 1933.

HAROLD R. MERWARTH, M.D., F.A.C.P.

#### DR. ROSWELL SCHIEDT FIDLER

Dr. Roswell S. Fidler, F.A.C.P., Associate Professor of Pathology at the Ohio State University College of Medicine, and Director of the Department of Clinical Pathology at White Cross Hospital in Columbus, Ohio, died Monday, June 30, 1952, aged 53 years. Dr. Fidler finally succumbed after a six-month illness to bronchogenic carcinoma.

Dr. Fidler received his medical degree from the College of Medicine, the Ohio State University, in 1925, following which he began his specialization in the field of his choice, pathology, under Dr. Ernest Scott at his alma mater. For a brief period he was pathologist to the Springfield City Hospital but soon returned to Columbus to become associated with the Department of Pathology at the University and to assume the Directorship of Laboratories at White Cross Hospital. He became a Diplomate of the American Board of Pathology, a Founding Fellow of the College of American Pathologists, a Fellow of the American Society of Clinical Pathologists, and a Fellow of the American College of Physicians in 1944. He was an active contributing member of the American Heart Association and he was active in the Ohio Society of Pathologists. Dr. Fidler was a veteran of World War I and served as a member of the Selective Service Medical Advisory Board during World War II.

Dr. Fidler was a constant guardian and champion of those moral and ethical principles which are the foundation stones of medical practice. He had an abiding conviction that the function of a private hospital, besides housing and caring for the sick, should be that of providing postgraduate medical education of the highest type to interns and residents. By his continuing interest and endeavors an unusually fine educational program was developed for intern and resident training at White Cross Hospital in Columbus. This was made easier through the close collaboration with the departments at the Ohio State University College of Medicine, where Dr. Fidler continued to serve in a teaching capacity to the undergraduate medical students. He maintained a constant interest in the progress of his science as it applied to better diagnosis and treatment in medicine, more particularly in the field of the cardiovascular diseases, and his bibliography shows a constant yearly contribution to the medical literature.

Most certainly Dr. Fidler was cut down in the prime of his medical career, and not only his family but his professional conferees, his patients, and his students have prematurely lost friend, counselor, and teacher.

CHARLES A. DOAN, M.D., F.A.C.P.,  
Governor for Ohio

#### DR. HAROLD INMAN GOSLINE

Dr. Harold Inman Gosline, F.A.C.P., was born July 2, 1888, in West Newton, Mass., and died July 18, 1952, in Provo, Utah, of acute myocardial failure.

A graduate of Harvard College and Harvard Medical School, Dr. Gosline had

formerly taught at Harvard Medical School, Brown University, Baylor University College of Medicine, Southern Methodist University and Columbia University College of Physicians and Surgeons. Dr. Gosline, whose specialties were pathology and psychiatry, had formerly been on the staff of the Danvers and Worcester (Mass.) State Hospitals, the New Jersey State Hospital at Trenton, the State Hospital for Mental Diseases, Howard, R. I., and Sing Sing Prison Hospital, Ossining, N. Y. He had also been Director and Chief Psychiatrist of the Dallas (Tex.) Child Guidance Clinic from 1923 to 1926, and had later become a member of the staff of the Bellevue Psychiatric Hospital. He was also connected with the Institute for Social Adjustment for seven years; and before becoming a Senior Physician at the State Hospital in Provo, he had served as Medical Officer at the Veterans Administration Hospital in Marion, Ind.; Staff Psychiatrist at the State Hospital in Butner, N. C., and as Clinical Director of the Woodward State Hospital and School in Woodward, Iowa.

During World War I Dr. Gosline was in the Medical Corps of the U. S. Army and was Pathologist at U. S. General Hospital No. 19, Oteen, N. C. A major, he was Commanding Officer of the Third Army Laboratories in Coblenz, Germany; and as a lieutenant colonel in the Reserves, he was Commanding Officer of the Sixth Hospital Center.

In addition to having memberships in various state and local societies, Dr. Gosline was a Diplomate of the National Board of Medical Examiners and the American Board of Psychiatry and Neurology. He was a Fellow of the American Medical Association and a member of the New England Society of Psychiatrists, the New York Society of Clinical Psychiatrists and the American Psychiatric Association. He had been a Fellow of the American College of Physicians since 1940.

#### DR. JOSEPH EMMET HIRSH

Dr. Joseph Emmet Hirsh, F.A.C.P., was born February 28, 1898, at Shenandoah, Pennsylvania, and died September 27, 1952. During his early childhood his family moved to Birmingham, where he obtained his primary and secondary education. He received his bachelor's degree from the University of Alabama in 1918, and was graduated from the University of Pennsylvania School of Medicine in 1922. Following internship and residency training at the Philadelphia General Hospital, he spent periods in 1926 and 1934 in study in Vienna. He entered practice in Birmingham in 1924 and soon became recognized as one of the leading internists of the southeastern area.

Dr. Hirsh became an Associate of the American College of Physicians in 1933 and a Fellow in 1936. He was a member of the American Heart Association and the American Medical Association. He was certified by the American Board of Internal Medicine in 1937. He was active in civic and religious circles, and was one of the outstanding clinical teachers at the Medical College of Alabama, being a full Professor in that institution. He was one of the leading spirits in the Medical Round Table discussion group in Birmingham. Aside from his devotion to his profession, his outstanding interests were people and sports. He was especially devoted to the football team of the University of Alabama and had missed only three games in twenty-four years. His death occurred suddenly on the Alabama bench at a particularly exciting moment in the contest with Louisiana State University. Had he been given the opportunity to choose, he would almost certainly have selected sudden unexpected exitus at such an occasion. Only a few of his friends knew that he had suffered from angina pectoris for nearly fifteen years and that during that time he had not only met unflinchingly his numerous professional and civic responsibilities but had also retained a serene and gay spirit. The many hundreds of patients he treated for angina had no inkling that he would have been justified in saying, "Alas, poor shepherd! Searching of thy wound, I have by hard adventure found mine own."

His love of people transcended even his fondness for sports and his devotion to medicine. This was reciprocated, and few men have had more friends. If the complexities of the modern world prevented his living in "a house by the side of the road," they only strengthened his rôle as "a friend to man."

TINSLEY R. HARRISON, M.D., F.A.C.P.

#### DR. OTIS BURGESS NESBIT

Dr. Otis Burgess Nesbit, F.A.C.P., was born in Severance, Kansas, January 31, 1871. He was a graduate in pharmacy of Valparaiso University; M.D. degree, Bennett Medical College in 1902; Valparaiso Christian Hospital, 1902-1910. He was Professor of Therapeutics, 1910, and Professor of Materia Medica, Pharmacy Department, 1906-13, at Valparaiso University. He was a member of the staffs of Mercy and Methodist Hospitals, and from 1902 to 1913 he practiced medicine in Valparaiso.

Gary, Indiana, was one of the first cities in the country to employ a full-time school physician. About this time (1910) Dr. Nesbit became interested in public health and became President of the Board of Health, Lake County Health Commission. He was Director of Medical Inspection, Gary Public Schools from 1913 until 1940 when he retired.

During the many years Dr. Nesbit served the children of Gary, he developed programs and technics that became patterns in the field of school health examination, follow-ups and so on. He was a strong advocate for the extensive use of school and public health nurses. Even though some of the doctor's ideas and programs were new and at times controversial, he was always respected by the profession and was active in his medical society. He was a past President and Secretary of the Porter County Medical Society, former Secretary of the Tenth District Medical Society; Councilor, Indiana State Medical Society; Censor, Lake County Medical Society; a member of the American Public Health Association; and a Fellow of the American College of Physicians since 1925.

Dr. Nesbit particularly loved the Dunes and was an authority on Lake County history and development of the Calumet region. In his later years he penned much information on the development of Lake County medicine, which will some day be of great value to the history of that fast growing and important industrial center.

Dr. Nesbit retired from active practice in 1945, and died March 18, 1952, at the University Hospital, Ann Arbor, Michigan, of coronary occlusion. Surviving him are two daughters, Miss Allegra N. Nesbit, Gary, and Mrs. Alexander Oppenheim, Singapore.

JAMES O. RITCHEY, M.D., F.A.C.P.,  
Governor for Indiana

#### DR. EMANUEL BARNETT SCHOENBACH

Dr. Emanuel Barnett Schoenbach, F.A.C.P., of Brooklyn, New York, died on September 6, 1952, of coronary thrombosis. He was born in New York City on November 11, 1911. He received a B.S. degree from Harvard University in 1933 and an M.D. degree from Harvard Medical School in 1937. Thereafter he served as an intern at the Mount Sinai Hospital in New York from 1937 to 1940. He was a Fellow and later an Instructor in Bacteriology and Immunology at Harvard Medical School and the Harvard School of Public Health from September, 1940, until January, 1942. He returned to Mount Sinai Hospital as Resident from January, 1942, to January, 1943. He then moved to Baltimore, where he became Assistant Attending Physician and later Physician in Johns Hopkins Hospital during the period from 1946 to 1951. He also served as Associate Physician in Sinai Hospital in Baltimore.

He was Consultant in the Clinical Research Unit of the National Cancer Institute and in Internal Medicine to the Veterans Administration Hospitals in that area. In 1951 he assumed the position of Director of Medical Services at Maimonides Hospital and Professor of Medicine in the State University of New York College of Medicine at New York City.

In 1941 Dr. Schoenbach served as a member of the Harvard Commission which was sent to Halifax, Nova Scotia, because of the epidemics of infectious diseases which were raging there at that time. He served as Consultant to the Secretary of War for Prevention of Epidemic Diseases in the Army and was Field Director of the Commission on Meningococcal Meningitis. He conducted investigations on diphtheria and diphtheritic polyneuritis in the Mediterranean and European Theatres and later became Assistant Administrator to the Army Epidemiological Board in 1945.

Dr. Schoenbach was a member of Sigma Xi and Alpha Omega Alpha, a Diplomate of the American Board of Internal Medicine, and had been a Fellow of the College since 1950. He was a member of the American Association for Advancement of Science, American Public Health Association, Massachusetts Medical Society, American Association of Immunologists, American Federation for Clinical Research, Society for Clinical Investigation, Johns Hopkins Medical Society, Society of Hygiene, Society for Experimental Biology and Medicine, and the Medical Research Club of Baltimore. He was also a Fellow of the American Medical Association and a Fellow of the New York Academy of Sciences.

Dr. Schoenbach was a man of outstanding ideals. He had recently assumed a post of great potential importance, and it was a matter of deep sorrow to his confreres and to those who welcomed him in his new responsibility, that he was lost to Medicine at the peak of his productive career.

IRVING S. WRIGHT, M.D., F.A.C.P.,  
Governor for Eastern New York

#### DR. EARL JESSE THOMAS

Dr. Earl Jesse Thomas, F.A.C.P., died at the age of seventy on May 23, 1952. Born in Findlay, Ohio, on October 7, 1882, Dr. Thomas gained his premedical college training at Ohio State University before seeking his medical degree at the University of Michigan Medical School, where he was graduated in 1905. He remained for his internship at the University Hospital in Ann Arbor and then returned directly to Findlay, where he became a member of the Medical Staff and Roentgenologist to the Findlay Home and Hospital, becoming Chief of the Medical Staff in 1928. Dr. Thomas served as Secretary and Treasurer of the Hancock County Medical Society in 1926, and held lifelong memberships in the Ohio State Medical Society and the American Medical Association, and early became a member of the American Roentgenological Society. He was admitted to Fellowship in the American College of Physicians in 1926.

Dr. Thomas worked faithfully and indefatigably in his local community until forced to retire November 1, 1947, after suffering a cerebral hemorrhage.

Dr. Thomas' life was one of service to his community and to the medical fraternity, of which he continued to be a worthy member throughout a long life of service.

CHARLES A. DOAN, M.D., F.A.C.P.,  
Governor for Ohio

#### DR. PHILIP WORK

Dr. Philip Work, F.A.C.P., was born in Fort Morgan, Colorado, June 20, 1888, and died in Las Cruces, New Mexico, July 1, 1952, where he had been assigned as a staff member of the Veterans Hospital.

He was graduated from the University of Pennsylvania School of Medicine in 1913, interned in what is now Corwin Hospital, Pueblo, did his residency in Philadelphia General Hospital in 1914 and 1915 and again in 1920, and later did post-graduate work in Vienna, Austria (1930). He was Acting Physician and Clinical Director, Woodcroft Hospital, Pueblo (1914-19); Consultant in Neuropsychiatry, Colorado Fuel and Iron Co. (1915-22); Neurologist, Colorado and Southern Railroad Co. (1920-35); District Neurologist, U. S. Veterans Administration (1919-22); Member of U. S. Pension Board, and was for a few years Secretary of the Colorado Board of Medical Examiners.

Among the societies of which he was a member were the American College of Physicians, American Neurological Association, the American Psychiatric Association, the Philadelphia Neurologic Society, the Central States Neurologic Society, and the Association for Research in Nervous and Mental Diseases.

Dr. Work had practiced his specialty of neuropsychiatry in Denver and was an active member of the staffs of most of the Denver hospitals. Before that he had practiced in Pueblo. Having served in both World Wars I and II, he attained the rank of Colonel and later served as Chief, Neuropsychiatric Service, Veterans Administration Hospital, Reno, Nevada (1946-48), later becoming Chief, Neurological Service, Veterans Administration Hospital, Gulfport, Mississippi.

Dr. Work was active in medical teaching, in which field he attained a Professorship and became Head of the Department of Neurology, University of Colorado School of Medicine. He was also Special Lecturer in Forensic Medicine, University of Denver Law School.

He was a member of Theta Delta Chi, Alpha Pi Omega and Sigma Xi fraternities, and had been a Fellow of the American College of Physicians since 1928.

His death marked the passing of the last doctor in Colorado bearing the proud name Work, he having been the elder son of the late distinguished doctor and statesman, Dr. Hubert Work.

CONSTANTINE F. KEMPER, M.D., F.A.C.P.,  
Governor for Colorado

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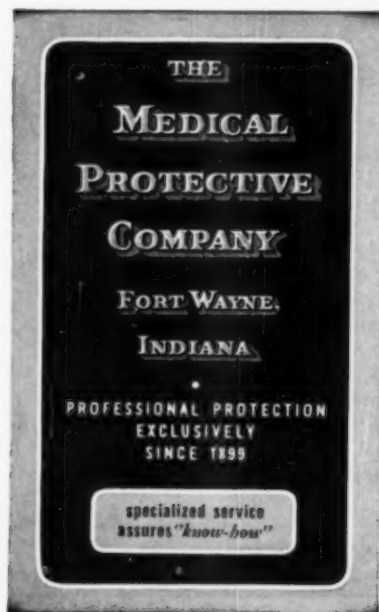
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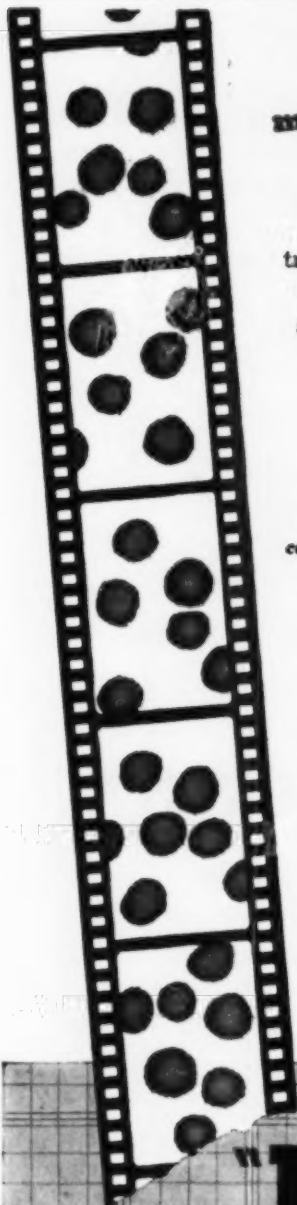
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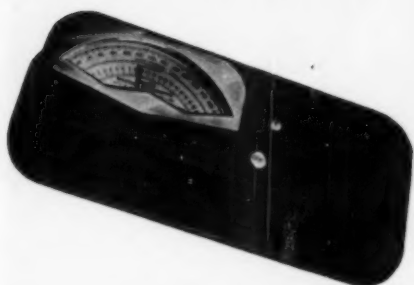
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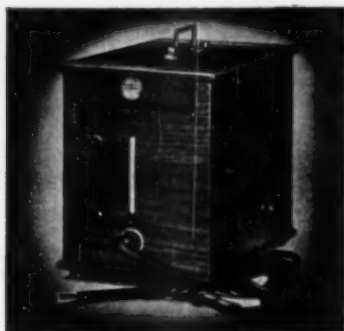
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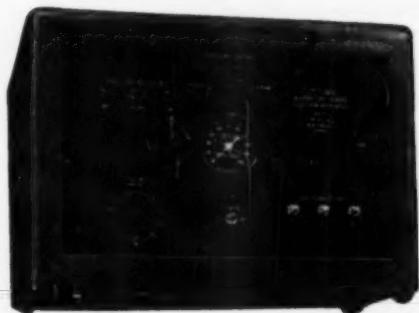
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